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SURGERY

A Monthly Journal Devoted to the Art and Science of Surgery

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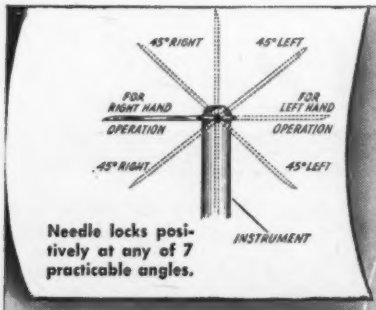

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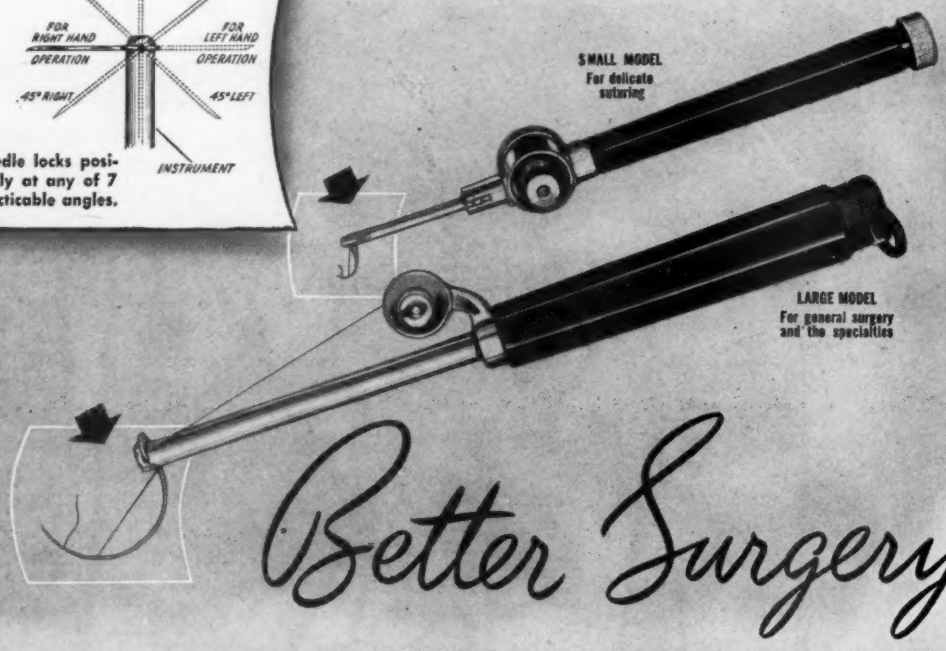

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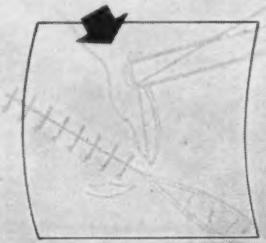

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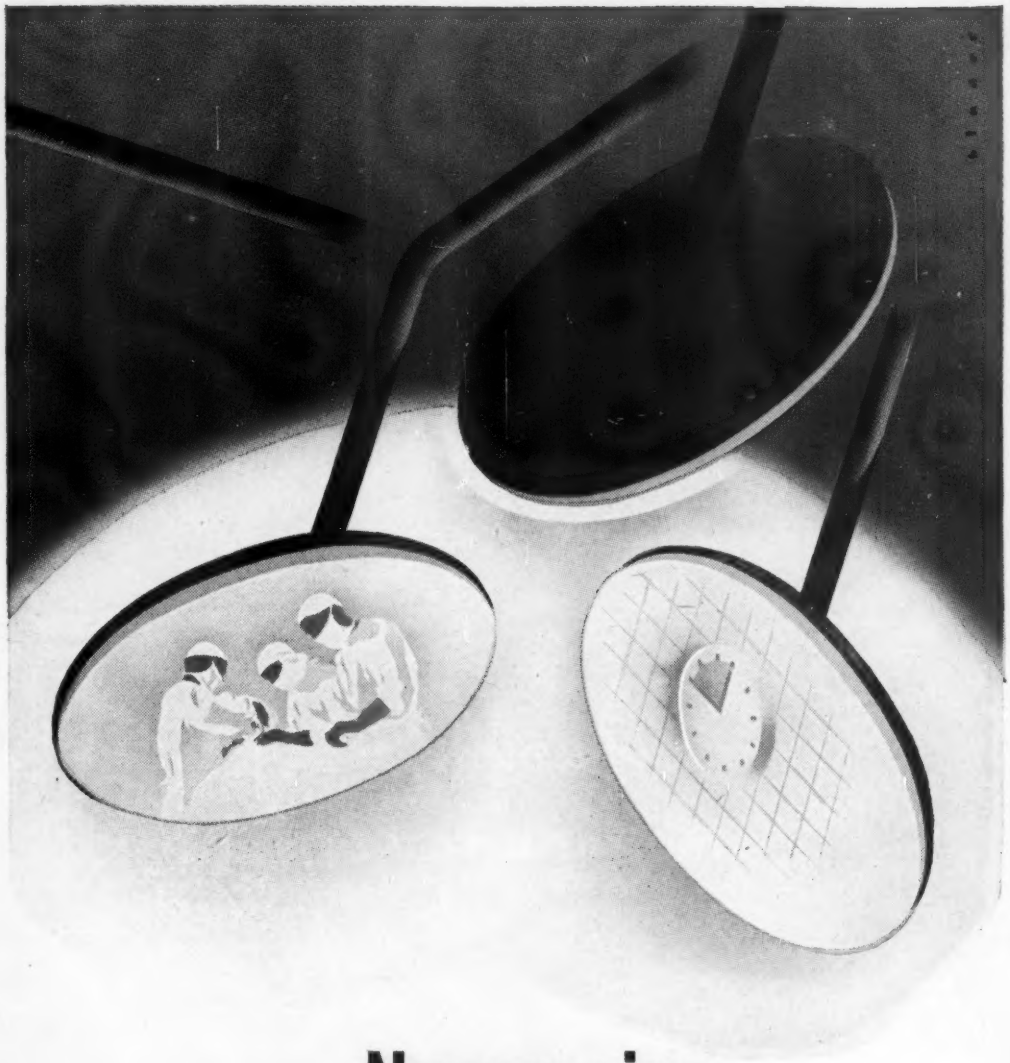

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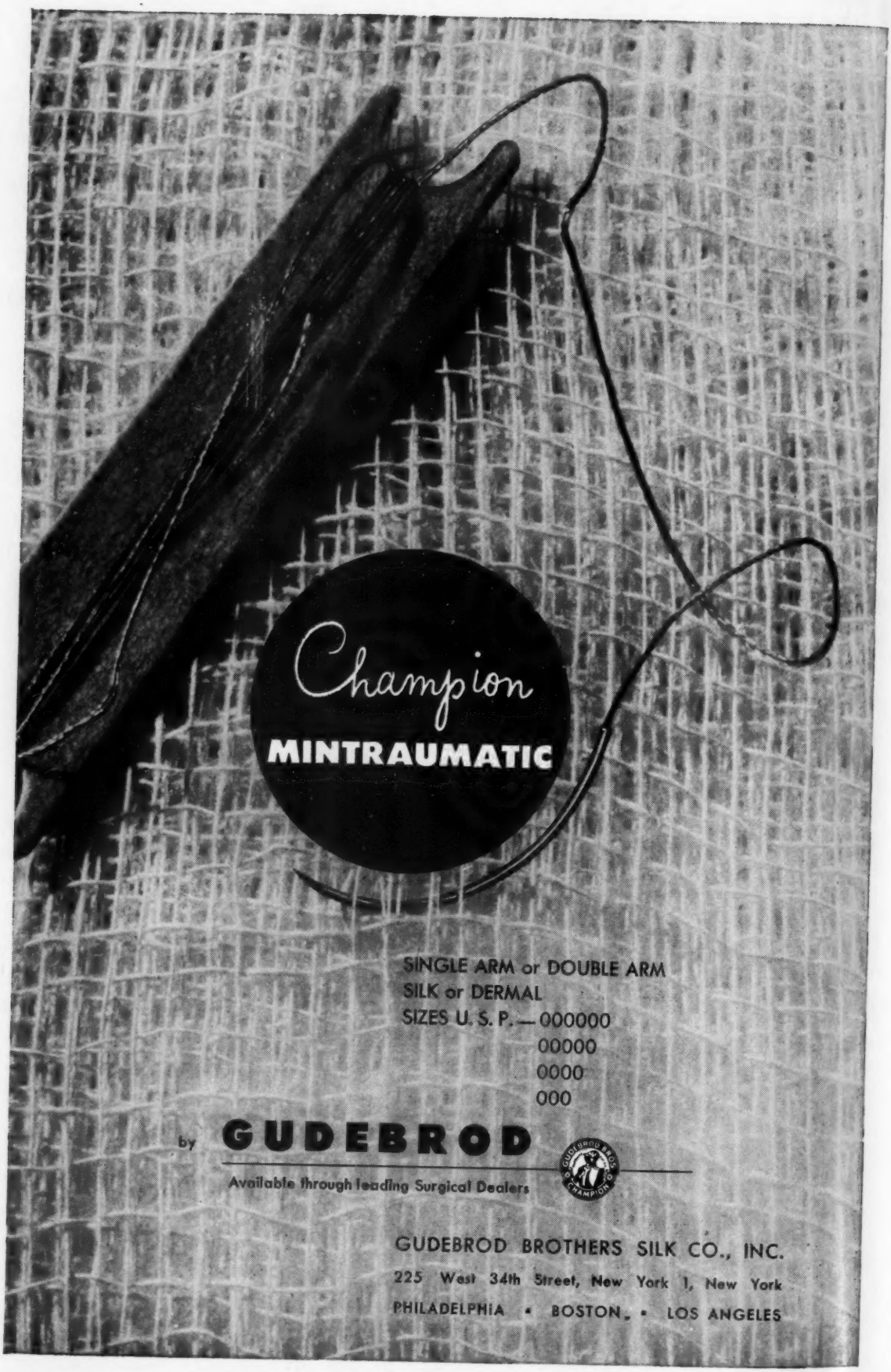
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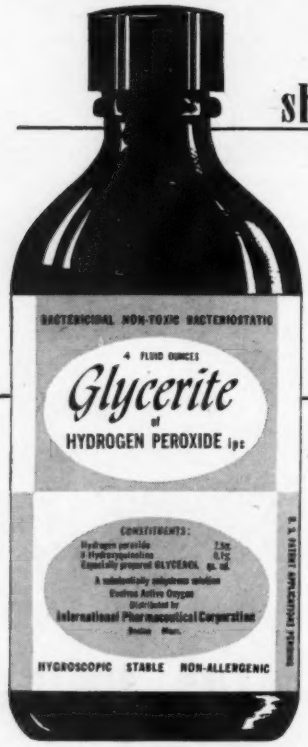

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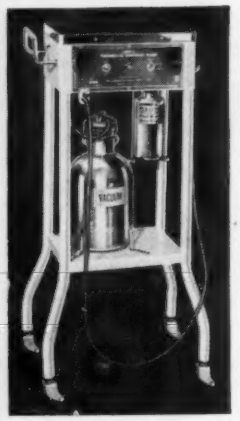

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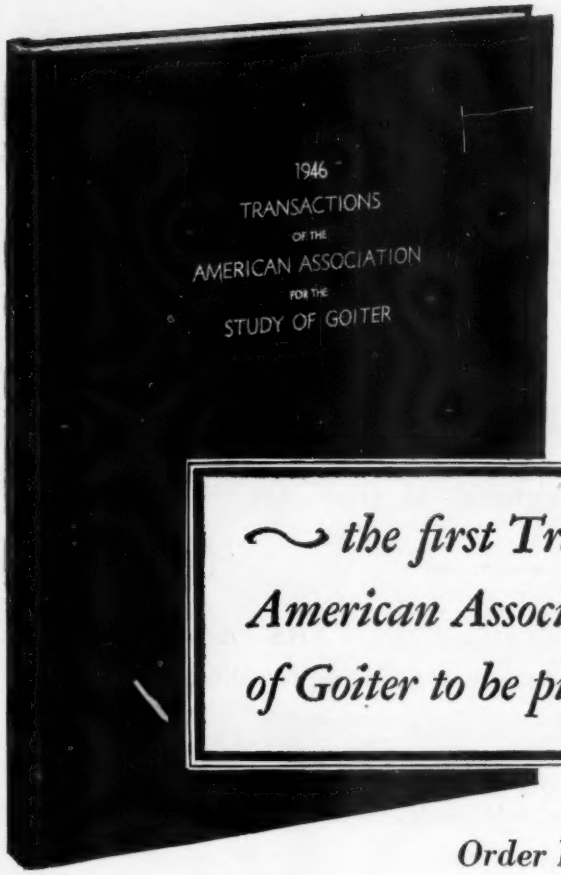

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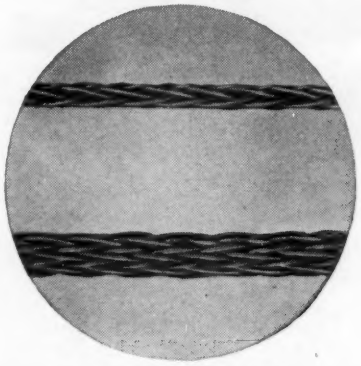

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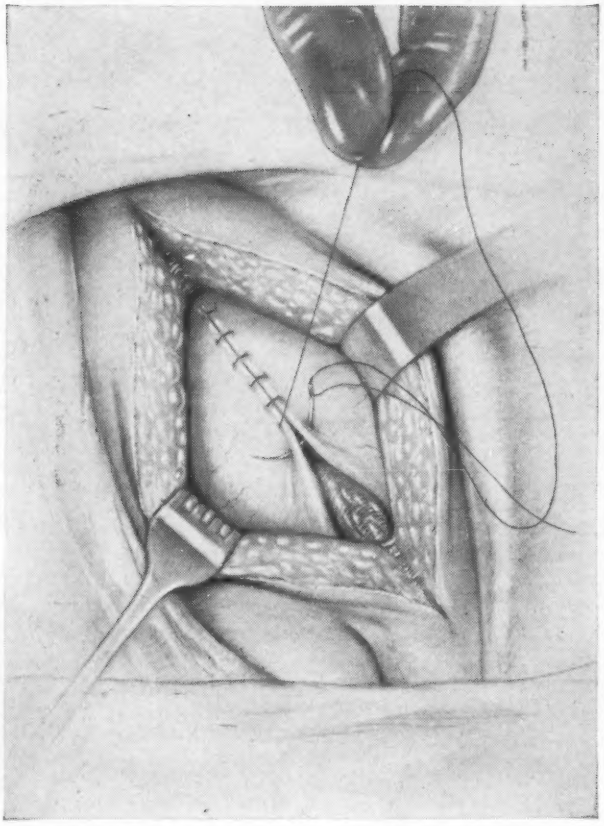

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BENIGN CENTRAL CARTILAGINOUS TUMORS OF BONE

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THIS communication is concerned with a study of a group of benign central tumors of bone which are derived from cartilage. It includes also the central chondromas and benign chondroblastomas which have been referred to in recent medical literature as "Codman's epiphyseal chondromatous giant cell tumors." The two groups will be considered separately.

CENTRAL CHONDROMA

The central chondroma or enchondroma is a benign lesion occurring mainly within the bone as contrasted with the osteochondroma or enchondroma which is chiefly cortical and projects beyond the normal confines of the bone. A series of twenty-two cases of central chondroma observed in the bone tumor department of Memorial Hospital forms the basis of this study.

Age.—Although central chondroma probably has a long latent period during which its presence is not suspected, it is usually noticed between the ages of 10 and 30 years (see Table I).

Sex.—Sex is of no apparent importance in this condition; twelve of the cases occurred in females and ten in males.

Bone Involved.—The long bones were affected in all cases and extremity bones accounted for all but one, a rib (see Table II).

More than one-third of the cases presented lesions of the phalanges and this is the most frequent tumor found in that location.

Clinical Manifestations.—Simple chondroma may be completely symptomless. When it has altered the contour of the bone the patient may notice swelling or deformity. Pain, when present, is generally inconstant and mild. Disability is infrequent. Pathologic fracture, especially in phalangeal chondromas, is often the incident which gives rise to the recognition of the condition. Trauma which results in the fracture is often trivial and nearly always less severe than that which is responsible for simple fractures through normal bone. There was a history of antecedent injury in eight cases which led to the discovery

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of the tumor. The usual history was that of an injury followed by pain, swelling, and ecchymosis. However, the triviality of the symptoms is indicated by the fact that the patients often delayed several years before seeking treatment.

Etiology.—As yet no completely satisfactory theory of the origin of central chondroma has been advanced. Disturbances in cartilage of a developmental nature may be an important factor. The concept that following injury to bone cartilage is found in the reparative process is not convincing as applied to the derivation of central chondroma.

Gross Appearance.—The surgeon seldom finds it difficult to identify this tumor at operation. It lacks the gross appearance of tissue seen in simple cyst, giant-cell tumor, or fibrous dysplasia. It presents a solid, whitish, firm tumor completely filling the cavity and has a slightly gritty feel when attempts are made to remove it with the curette. At times calcific particles are seen and felt but it lacks the purely fibrous quality of fibrous dysplasia, the vascular reddish nature of giant-cell tumor, or the fluid-filled spaces of simple cyst. Myxomatous changes are not uncommon and it is probable that the extremely rare cases of pure myxoma of bone which have been reported are examples of degeneration of a central chondroma. While not encapsulated the lesion is usually rather definitely circumscribed and for this reason it is possible to remove it completely by painstaking curettage.

Microscopic Findings.—The histologic appearance of this tumor is so characteristic that it should offer little difficulty to the experienced pathologist. Hyaline cartilage predominates. The cells are usually rounded but may vary in size and may become fusiform or stellate. Calcification may be seen in scattered areas.

Since there is a distinct tendency toward secondary chondrosarcomatous change and because this may not be evident in all parts of the tumor, it is

TABLE I

AGE (YEARS)	NUMBER OF CASES
Under 11	1
11 to 20	6
21 to 30	9
31 to 40	3
41 to 50	1
51 to 60	0
61 to 70	1
71 to 80	1
Total	22

TABLE II

BONE INVOLVED	NUMBER OF CASES
Phalanx	8
Femur	4
Tibia	4
Humerus	2
Fibula	1
Metacarpal	1
Rib	1
Multiple (phalanges, metacarpal, fibula)	1
Total	22

necessary to bear in mind that a report of "benign chondroma" based on an examination of only a portion of the entire tumor can be misleading. It is, of course, obvious that a microscopic study should invariably be made of all portions of the tissue removed from any central bone lesion (Fig. 1).

X-Ray Findings.—While the roentgenologist can frequently make a strong presumptive diagnosis of a central chondroma on the basis of a circumscribed area of radiolucency in the end of a long bone it is often possible to confuse the picture with that presented by bone cyst, giant-cell tumor, and nonosteogenic fibroma of bone. We have seen cases in which a roentgenographic diagnosis of giant-cell tumor was made without a biopsy and prolonged roentgen

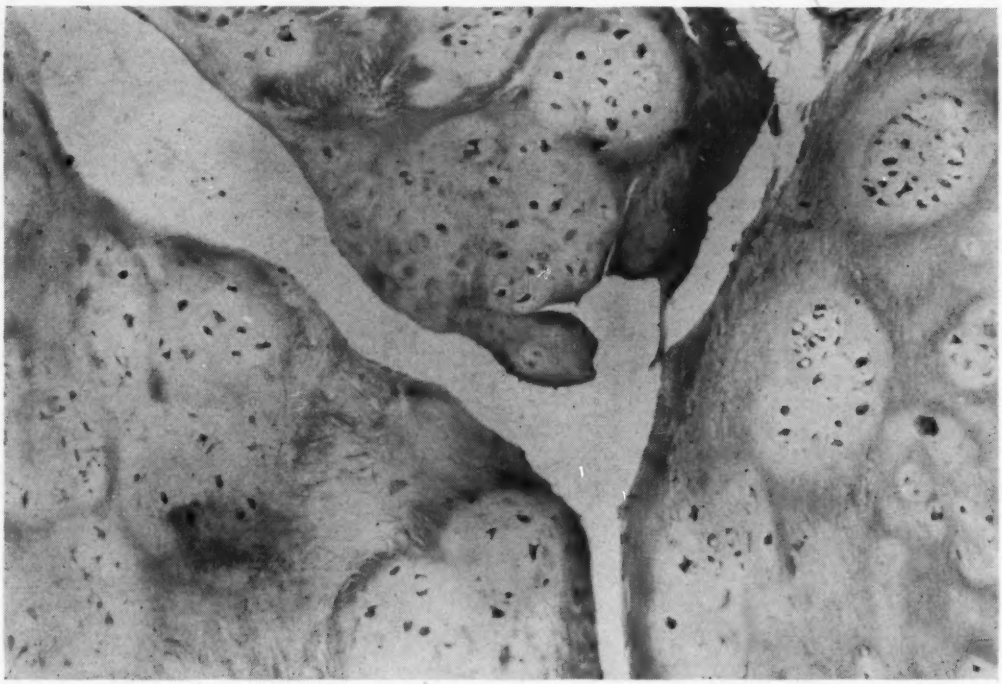

Fig. 1.—Histologic appearance of benign chondroma. Cartilage cells are lying in a matrix of hyaline material. The cells are uniform in size, shape, and nuclear staining.

therapy given without apparent improvement; by the time the diagnosis of chondroma was confirmed by late histologic examination, the effect of the radiation was such as to render a surgical attack impractical or actually hazardous. We believe, therefore, that any accessible central bone lesion deserves an exploration and complete extirpation by surgical means. This method assures a microscopic diagnosis and, most important, gives satisfactory results regardless of whether the condition is one of cyst, chondroma, or giant-cell tumor. In certain instances a central chondroma may closely resemble a chondrosarcoma or an osteolytic osteogenic sarcoma and it is, therefore, imperative that this issue be clearly decided before radical surgery is instituted.

Treatment.—The treatment of central chondroma is surgical. For lesions in the rib, fibula, and scapula, resection of the entire tumor-bearing area is indicated. In the majority of cases involving other bones this will not be

practical and it is not essential since a thorough curettage with adequate exposure obtained by unroofing the cavity will yield satisfactory results.[6] When the involved area constitutes a considerable proportion of the thickness of the shaft of an essential long bone (femur, humerus, tibia, etc.) it is important to utilize bone chips obtained from the ilium or pencil grafts from the tibial cortex to fill the defect and to assure more complete and more rapid bone regeneration.

In occasional cases where curettage has been followed by one or more recurrences, a segmental resection is an alternative to an amputation.

Recurrences will take place if the removal is incomplete, but in this series only two of the twenty-two patients had a recurrence and both have been successfully managed by reoperation.

Four patients received roentgen therapy. In three of these (two lower femur and one upper tibia) the response was so unsatisfactory that a mid-thigh amputation had to be performed in two, while in the third an aspiration biopsy disclosed that the condition had become sarcomatous. The fourth patient received preoperative irradiation of a rib tumor which was then resected.

TABLE III. TREATMENT OF CENTRAL CHONDROMA

METHOD EMPLOYED		NUMBER OF CASES
Roentgen-rays only		0
Surgery only		17
Excision	2	
Curettage only	6	
Curettage plus chips or transplants	6	
Resection	2	
Amputation	1	
Roentgen-rays and surgery		4
Amputation	3	
Resection	1	
Operation (curettage) elsewhere		1
Total		22

Complications.—The course of these cases was singularly devoid of complications. Primary wound healing occurred in every instance and no late imperfections were observed. Pathologic fracture occurred in one case (metacarpal) while the patient was catching a baseball.

The end result was classified on an anatomic, functional, and economic basis. With a few exceptions, two cases too recent for evaluation, three patients who died, and one in which amputation was performed, the results were uniformly good. The follow-up extended from one to fourteen years; in eight cases follow-up was for five or more years and in five of the latter for more than ten years.

CASE REPORTS

CASE 1.—A. C., a 27-year-old woman, was admitted to Memorial Hospital on Sept. 13, 1930, with a history of intermittent pain over a period of four years. The first roentgenographic examination, made three months prior to admission, revealed a "cystic area in the middle third of the left humerus." There had been no previous surgical or radiation therapy. Local examination revealed a smooth, tender, spindle-shaped swelling of bone.

Following a curettage on Sept. 25, 1930, a pathologic diagnosis of central chondroma was made. Ten months later a recurrence was noted and a second curettage was performed on July 23, 1931, following which the pathologist reported atypical mucinous granulations, chronic osteitis, callous.

The patient remained practically symptom-free for eight years, at the end of which time the pain recurred. Roentgenograms revealed reactivity in the mid-humerus. She was readmitted to the hospital on June 4, 1934, for a third operation which consisted of an extensive exposure of the tumor-bearing area, and curettage. The pathologic diagnosis was that of degenerating chondromyxoma. As usual the wound healed per primam.

The patient again remained symptom-free for two and one-half years, when, because of pain and roentgenographic evidence of a recurrence, it was decided that a segmental resection of the mid-portion of the humerus was indicated. The fourth operation, performed on Jan. 18, 1936, consisted of resection of the middle third of the humerus with substitution of a massive tibial transplant for the defect. Following the operation, splenic extract was administered orally. The arm was immobilized with plaster shoulder spicas,

Fig. 2.—*A*, Central chondroma of humerus following three failures to control by curettage; lesion of borderline malignancy. *B*, Appearance immediately after segmented resection and substitution of massive tibial transplant dowelled at either end. *C*, Appearance eighteen months after operation. Ten years later the patient has excellent function, pursues former occupation as typist, and is free from any evidence of disease.

changed occasionally, for the next seven months. Thereafter physiotherapy was instituted and a special brace was made to support the limb. Roentgenograms revealed solid union of the transplant to the upper and lower portions.

One year after the fourth operation the patient returned to work as a typist and she has worked steadily for the past ten years. There has been no further return of the disease (see Fig. 2).

CASE 2.—P. B., a man aged 29 years, was admitted to Memorial Hospital on Oct. 15, 1940, with a history of having sustained a crushing injury to the tip of the right thumb four years previously. The pain, swelling, and ecchymosis subsided but the thumb remained enlarged. Six weeks prior to admission he struck the tip of the same thumb.

Fig. 3.—Chondroma of mixed type. The tumor is partly central, partly osteochondromatous. The patient was a soldier and had remarkably little impairment of function. The symptoms, though of long duration, were mild.

Roentgenograms revealed a central osteolytic expansile tumor of the terminal phalanx with pathologic fracture. Operation performed on Oct. 16, 1940, consisted of curettage and the introduction of tibial transplants in the cavity. The wound healed per primam. Pathologic diagnosis was that of central chondromyxoma.

Roentgenographic examination on Feb. 11, 1941, revealed a practically normal contour of the thumb, no pain or disability, and healing. The patient was last seen five and one-half years after the operation; the anatomic and functional result had remained excellent.

CASE 3.—N. L., a 71-year-old man, was first seen at Memorial Hospital on March 3, 1943. He gave a history of pain and disability on flexion of the right knee over a period of five months. Six weeks prior to admission he had noticed a swelling on the anterior aspect of the lower third of the right thigh. Roentgenographic examination made else-

where showed what was diagnosed as metastatic carcinoma. Physical examination revealed a firm, nontender mass measuring 18 cm. situated on the anterior aspect of the lower third of the right thigh. Flexion was impaired beyond 80 degrees.

A review of the submitted roentgenograms disclosed a large irregular area of bone destruction in the lower end of the shaft of the left femur above the condyles indicating a primary bone tumor apparently medullary in origin.

An aspiration biopsy was done on March 11, 1943, and the report was some type of cartilaginous tumor—the material largely cartilage and with almost no cells. Following a second aspiration biopsy on March 24, 1943, the report was chondroma, and a third aspiration on March 31, 1943, was reported as fully malignant osteogenic sarcoma.

Roentgen therapy was instituted on March 15, 1943 (before the diagnosis of sarcoma was established). A total of 1,500 r. at 250 kv. and 70 cm. target skin distance was given to each of two portals 24 by 15 cm. On April 17, 1943, a high thigh amputation was performed

Fig. 4.—Extensive central chondroma. The patient was an adult colored man. This case was considered malignant on clinical and roentgenographic grounds and an amputation was performed; its extent precluded a resection or a curettage. Tumors such as this have definite malignant potentialities. Patient was well nine years later.

and the pathologist reported osteogenic sarcoma on basis of an old central chondroma. The patient made an uneventful recovery. The diabetes which was discovered preoperatively was well controlled. Pulmonary metastasis developed and he died eight months after the operation.

BENIGN CHONDROBLASTOMA

Benign chondroblastoma (Codman's epiphyseal chondromatous giant cell tumor) remained a confusing entity for years prior to its description by Codman, the founder and first registrar of the Bone Sarcoma Registry. He recognized it as a benign lesion and was aware of its cartilaginous nature but believed it belonged in the giant-cell tumor group.

Fig. 5.—Chondroma of femur. The patient, a young adult man, had a fifteen-year-history of mild pain. Despite a lack of microscopic confirmation the roentgenographic appearance is typical of chondroma.

We have long felt that it is not a giant-cell tumor and that it belongs properly with the tumors of cartilaginous origin. Jaffe and Lichtenstein considered it to be distinct from giant-cell tumor and not even a variant of it. They termed it a benign chondroblastoma. Little would be gained here by repeating the description and arguments; those interested should read the original article.

We are presenting eight cases of this condition observed in the bone tumor department of Memorial Hospital prior to Jan. 1, 1946.

Age and Sex.—As shown in Table IV, four of our cases were in the age group from 11 to 20 years, while all of the cases of Jaffe and Lichtenstein were in this decade.

Again, in contrast to their series, which were all males, ours showed the sexes to be equally divided, that is, four males and four females.

Location of Bone Involvement.—Codman's original description covered a small number of cases all involving the upper end of the humerus; however,

TABLE IV

AGE (YEARS)	NUMBER OF CASES
Under 11	1
11 to 20	4
21 to 30	1
31 to 40	1
41 to 50	0
51 to 60	1
Total	8

cases were soon reported showing the lesion to be by no means confined to that locality. Jaffe and Lichtenstein considered that they probably begin in the epiphysis and involve the metaphysis secondarily. Our experience supports this assumption.

TABLE V

BONE INVOLVED	NUMBER OF CASES
Femur	3
Humerus	2
Tibia	1
Metacarpal	1
Astragalus	1
Total	8

Clinical Manifestations.—Pain and swelling at the site of the lesion is the usual complaint. Trauma has not been shown to be of etiologic importance although an injury to the part might well attract the patient's attention to it. Only two of our eight patients gave a history of antecedent injury and in neither did there seem to be any convincing evidence of a causal relationship. The correct diagnosis was arrived at only once prior to receipt of the pathologist's report.

Pathology.—According to Jaffe and Lichtenstein the tumor is derived from cartilage germ cells or chondroblasts. Calcification of the necrotic matrix in irregular areas is a distinctive feature of the disease but this has not been present in recognizable degree in some of our cases. The giant-cell elements, responsible in the past for the inclusion of this neoplasm among the giant-cell tumors, are multinuclear macrophages. They may appear in the hyaline chondroid tissue, in areas of hemorrhage, and around vascular sinuses.

Treatment.—Perhaps because of their more primitive cellular pathology these tumors are somewhat radiosensitive, certainly more so than are ordinary chondromas. Hence, there is a possibility that roentgen therapy may be an entirely acceptable method of treatment. However, since an operation is usually necessary to establish the diagnosis and since conservative surgical measures have proved satisfactory, we regard surgery as the method of choice. One may deal with these tumors much as with the giant-cell tumor or the central chondroma; if the removal is thorough the results are satisfactory.

TABLE VI

METHOD EMPLOYED	NUMBER OF CASES
Roentgen rays only	3
Surgery only (curettage)	5
Total	8

CASE 4.—T. T., a girl 13 years of age, was admitted to Memorial Hospital on Nov. 14, 1945, complaining of persistent pain in the medial side of the left knee of six months' duration. The pain was more intense at night or when walking or standing for long periods. Two months after the onset she was told that it was a sprain and was treated with warm compresses. Three months after the onset roentgenograms were taken which were said to be negative. Finally a roentgenogram was made which showed an area of

Fig. 6.—Dyschondrodysplasia. At the site of the profound structural changes in the upper femoral region a secondary chondrosarcomatous degeneration has developed. The long bones of the entire lower extremity showed the characteristic features of hereditary deforming dyschondroplasia. The condition was inoperable and caused the patient's death.

decalcification in the medial condyle of the left femur. Physical examination on admission disclosed practically nothing more than a slight degree of tenderness on the medial aspect of the left femur in the condylar region and a 1 cm. increase in circumference at this level as compared with the normal side. Roentgenograms revealed a cystic area of bone destruction in the medial condyle of the femur measuring about three-quarters inch in diameter. Roentgenograms made over a period of several months showed a slight in-

Fig. 7.

Fig. 8.

Fig. 7.—Fibrous dysplasia; the appearance is suggestive of central chondroma.
Fig. 8.—Benign chondoblastoma; curettage was successfully employed.

crease in the size of this area. According to the roentgenologist a diagnosis of chondromatous giant-cell tumor was the more likely one.

On Nov. 28, 1945, an operation was performed as follows: through a transverse incision a window was made in the outer shell of the medial condyle measuring 1 cm., giving access to the cavity which was immediately curetted. It was then swabbed with zinc chloride and flushed with normal saline solution following which it was filled with chips taken from the window; the wound was closed in layers without drainage. Primary wound healing took place. The pathologist reported Codman's chondromatous giant-cell tumor (chondroblastoma). The postoperative course was uneventful. The patient was last seen on July 10, 1946, at which time she was living a completely normal existence. The wound was well healed and movements of the knee were complete.

A. *B.*

Fig. 9.—Benign chondroblastoma (Codman's epiphyseal chondromatous giant cell tumor). *A*, The extent of the lesion and its sharp limitation at the epiphyseal line; *B*, a bone regeneration and satisfactory healing following curettage of the involved area.

CASE 5.—B. M., a 9-year-old girl, was admitted to Memorial Hospital on Oct. 22, 1943. The chief complaint was pain in the upper end of the right leg of eight months' duration; two months after its onset a swelling was noticed which persisted afterward. The child was rather poorly nourished, somewhat emaciated, and physical examination did not reveal anything significant beyond that of the local condition. In the upper end of the right tibia was a tender, fusiform swelling measuring 8 by 6 cm., the skin over which was

normal. There was no alteration in the knee-joint function, but there was some atrophy of the muscles of this extremity. The roentgenographic appearance of the lesion in the upper end of the right tibia was cystlike and it was diagnosed by the roentgenologist of Memorial Hospital as a Codman's tumor. Operation on Oct. 21, 1943, consisted of curettage and insertion of a tibial bone graft from the opposite tibia. The tumor was found to lay directly beneath the periosteum at one point and it was unnecessary to divide the bony cortex in order to gain access to it.

Pathologic report was atypical case of Codman's epiphyseal chondromatous giant-cell tumor (benign chondroblastoma of bone).

This patient was followed over a period of more than two and one-half years; meanwhile successive roentgenograms showed that the lesion healed satisfactorily and there was no evidence of a recurrence.

SUMMARY

1. Records of twenty-two central chondromas and eight chondroblastomas have been studied and conclusions have been presented.

2. The long bones are predominantly involved in both conditions; both are essentially diseases of youth and early adult life.

3. Pain and swelling are the most frequent initial complaints.

4. Chondroblastoma more closely resembles giant-cell tumor than does central chondroma. At times chondroblastoma presents roentgen evidence suggestive of a malignant bone sarcoma.

5. Surgical measures are applicable to both conditions. Roentgen therapy may be successful in chondroblastoma but it is not of value in central chondroma.

6. Chondroblastoma is neither a variant of giant-cell tumor nor is it confined to the upper humerus.

7. Cartilage tumors may remain benign but they may also become malignant, metastasize, and cause death.

8. Chondroma and chondroblastoma should never be regarded as inconsequential conditions that can safely be ignored. Whenever possible they should be removed surgically.

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CLINICAL EVALUATION OF BOVINE SERUM ALBUMIN AS A BLOOD SUBSTITUTE

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WORLD WAR II accentuated the need for a satisfactory blood substitute. This need, however, is not entirely related to military surgery, for the use of whole blood, plasma, and serum in civilian practice has become much more extensive since the principles of the prevention and treatment of shock and contracted protein stores have become better appreciated.

Although human blood plasma, and serum are, on general physiologic grounds, the most ideal transfusion fluids, still the difficulty in obtaining and storing them in large quantities makes them far from ideal from a practical point of view. A blood substitute derived from bovine blood, provided it were satisfactory in other respects, because of its practically unlimited source would thus obviate all difficulties associated with the procurement from a human source. Also, Cohn[29] felt "that the most effective materials for transfusion will often prove to be concentrates from blood—including concentrated red or white cells—of the components with specific physiological functions which are deficient in any given clinical condition."

The use of bovine plasma and serum has not found wide use, for it was felt that they were toxic to man. A review of the literature, however, reveals only the scarcity of factual data on this point. Shortell, Cotting, and Leary[1] reported, in 1916, on the use of bovine plasma principally in the topical application to wounds. Penna and associates[2] in 1917 used bovine serum intravenously and intramuscularly in the treatment of anthrax, with some good results. In 1921, Krause and co-workers[3] injected 198 children intravenously and intramuscularly with diphtheria and tetanus antitoxin prepared from cows. The amounts injected varied from 5 to 50 c.c. and the incidence of serum sickness was 6 per cent. Approximately eight years ago, exploration of the thesis that bovine plasma might serve as a blood substitute in the treatment of hemorrhagic shock and other states was begun in this surgical clinic.[4, 5] In a series of papers it was shown that bovine plasma could be given intravenously to man with relative safety, although the incidence of immediate reactions was approximately 50 per cent and that of delayed reactions between 47 and 60 per cent.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, from the Office of Scientific Research and Development and the University of Minnesota Medical School.

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By adsorbing bovine serum on human red blood cells, the incidence of immediate reactions was reduced to approximately 24.5 per cent, but the number of delayed reactions was not materially lessened.

In an effort to determine the source of the reactions Kremen, Taylor, and Hall[6] fractionated whole bovine plasma by ammonium sulfate precipitation and skin tested individuals to these fractions as well as to whole bovine plasma. They found that albumin caused the least number of positive reactions, the globulin was intermediate, and the whole plasma caused the largest number of positive reactions as well as those of greatest magnitude.

At the request of Dr. W. Cannon* and Dr. D. Edsall,† Cohn and co-workers undertook an investigation to determine whether plasma of animals could be made safe for human transfusion. Their earliest attempts at fractionation of bovine plasma were by the ammonium sulfate precipitation method,[7] but materials so obtained were used only to correlate the "salting out" procedures with other methods which were being investigated and were not intended for clinical testing. Cohn and his co-workers recognized that the ammonium sulfate precipitation method which had been in use for almost a century, and to the understanding of which they had so largely contributed,[7] would prove to be inadequate for the preparation in large amounts of proteins, purified, concentrated, and rendered safe for intravenous injection. New methods for the fractionation of plasma in alcohol water mixtures, at low temperatures, and controlled pH, protein, and salt concentration were developed by the Harvard group during the spring and summer of 1940.[8 10] Highly purified bovine serum albumin preparations so obtained proved similar to human serum albumin in such physiochemical properties as molecular size and shape, and osmotic efficiency, but differed slightly from human serum albumin in solubility and in amino acid composition, and could be readily differentiated by immunologic procedures such as precipitation reaction. Janeway and Beeson[11] injected this highly purified bovine serum albumin fraction into sixteen human subjects with three very mild immediate reactions and only two delayed serum sickness reactions. In June, 1941, Cohn and Hughes, Jr., were for the first time able to accomplish crystallization of bovine serum albumin.[12] Keys, Taylor, and Savage[13] stated in a letter that they had separated the albumin fractions from bovine plasma by precipitation with ammonium sulfate, ammonium phosphate, and alcohol, and found that bovine serum albumin gave far less reactions than did whole bovine plasma when injected into human beings.

Other investigators also felt that the antigenicity of bovine plasma or serum resided primarily with the globulin fraction and attempted to separate off the albumin portion. Davis, Eaton, and Williamson[14] injected thirteen patients with bovine serum albumin precipitated with saturated ammonium sulfate solutions without immediate reactions.

Lewis[15] and Edwards[16] attempted to remove the antigenicity of whole bovine plasma by despeciation. The former treated bovine plasma with 0.5 N so-

*Then Chairman of the Committee on Blood and Transfusions of the National Research Council.

†Then Chairman of the Medical Advisory Committee of the American Red Cross.

dium hydroxide at 37° C. for one hour; the latter heated bovine serum to 72° C. and prevented coagulation of the serum proteins by the addition of 0.2 per cent liquor formaldehyde and 0.2 per cent 0.880 N ammonia. Edwards[17] injected twenty-six individuals, with only three immediate reactions and no delayed reactions.

MATERIALS AND METHODS

The bovine serum albumin solutions used were supplied by Cohn and Hughes, Jr., of the Harvard Medical School, and Dr. J. D. Porsche* and Dr. J. B. Lesh.* Those made available to us by Porsche and Lesh were prepared and tested in collaboration with the Harvard group. During the initial testing period (Series A v.i.) the character of the preparation was continually changing as improvements in the method of preparations were found. However, the later preparations as tested in Series B, C, D represented a chemically uniform product of bovine serum albumin which had been crystallized four times from ethanol-water mixtures of controlled pH, temperature and ionic strength.[9, 10, 12]

In series C were included preparations of respectively first and second crops of crystals. However, as statistical evaluation showed no clinical difference, only the summary of the total experience is here reported.

All preparations in Series B, C, D were received as sterile ampules, containing 25 Gm. of albumin dissolved in 100 c.c. of saline solution and neutralized to pH 6.6. A preservative (merthiolate) which had been used in Series A was discontinued in the later series because of fear it might enhance the antigenicity of the preparations. Bacteriologic studies failed to reveal contaminating bacteria in any of these preparations. All preparations were of proved low globulin content and, excepting Series A, were of high stability. They were free of pyrogens by rabbit thermal test and were nontoxic to guinea pigs. Analysis of the more pertinent physical and chemical properties of crystallized bovine serum albumin at the Harvard Plasma Fractionation Laboratory revealed the following: globulin (by precipitin test), 0.05 per cent; carbohydrate (orcinol test), 0.1 per cent; nitrogen (micro-Kjeldahl), 16.0 per cent; molecular weight (from osmotic pressure), 69,000.

The patients used in this study were from the surgical services of the University Hospitals. In the earlier periods of this investigation only patients with advanced malignancies were employed, but as it became apparent that the albumin solutions could be given with no fear of immediate reaction, only individuals who were in good physical condition, afebrile, and who had no history of allergy were injected. Prior to administration the blood pressure, respirations, and temperature of the patient were obtained. In the earlier parts of this study a skin test (0.05 c.c. of $\frac{1}{10}$ dilution of bovine serum albumin solution intracutaneously, 1.25 mg.) was applied but for reasons to be given, this practice was abandoned later. Ten cubic centimeters of blood were drawn into a nonoxalate tube and set aside in an icebox for several days, after which the serum was drawn off in a suitable container, labeled, and kept. This was done so that if a delayed reaction occurred, immunologic differences could be determined between the patient's serum prior to injection and during and following

*Of the Armour and Company Laboratories, Chicago, Ill.

the period of delayed serum sickness. A syringe containing 5 c.c. of 1/1000 adrenalin hydrochloride was kept at the bedside while the patient was being studied, so that it could be given immediately if any untoward reactions were encountered. The unit of bovine serum albumin employed was 25 Gm. It was diluted to 200 c.c. with normal saline solution, given intravenously by the gravity drip method at a height of about four feet and at a rate such that the injection took between twenty to forty minutes. The patient's temperature, pulse, respirations, and blood pressure were checked every fifteen minutes for the first hour and then every one-half hour for three hours after the transfusion. The patients were then checked at intervals of three and six weeks after the injection both by questionnaire and return visit to the clinic. If no untoward reactions were detected by these means, the patients were considered not to have developed delayed serum sickness reaction. If the patient, however, developed a reaction, he was hospitalized and complete blood and urine analyses as well as electrocardiogram, capillary fragility, prothrombin levels, and phenolsulfonphthalein kidney function tests were obtained.

Samples of blood were drawn whenever possible at the beginning, at the height of, and one month after the subsidence of the delayed serum sickness. These along with the preinjection sample were forwarded to Janeway of The Children's Hospital at Boston for immunologic studies.

OBSERVATIONS

For reasons stated previously, the patients injected were placed in four series: Series A (patients injected from October 1941, to February, 1943), Series B (patients injected from April, 1943, to July, 1943), Series C (patients injected from September, 1943, to September, 1945), and Series D, covering the same time interval as Series C but consisting of patients who had one previous injection of bovine serum albumin and subsequently were reinjected.

Series A (October, 1941, to February, 1943).—In all, 82 patients received 135 injections with eight immediate reactions (9.7 per cent) and nine delayed reactions (10.8 per cent). (See Table I.)

The immediate reactions were of two main types (1) anaphylactoid, characterized by dyspnea, urticaria, cyanosis, and a fall in blood pressure and (2)

TABLE I. INCIDENCE OF IMMEDIATE AND DELAYED REACTIONS

SERIES	NO. OF PATIENTS INJECTED	NO. OF INJECTIONS	IMMEDIATE REACTIONS		IMMEDIATE REACTIONS OF PATIENTS INJECTED		DELAYED REACTIONS OF PATIENTS INJECTED	
			PYROGENIC	ANAPHYLACTOID	TOTAL NO.	PERCENTAGE	TOTAL NO.	PERCENTAGE
A	82	135	6*	2	8	9.7	9	10.8
B	57	60	0	0	0	0	7	12.3
C	232†	232†	3‡	0§	3	1.3	20‖	8.5
D	39	42	0	1	1	2.6	2	5 2
Total	410	469	9	3	12	2.9	38	9.2

*In one case sporeformer cultured from fluids.

†Eight injections with bovine serum albumin preparation AMB_1 and 29 injections with bovine serum albumin preparation AMB_2 not included.

‡Probably due to pyrogens in diluents or rubber tubing.

§One severe anaphylactoid reaction following bovine serum albumin preparation AMB_1 not included.

‖Two moderately severe delayed reactions following the injection of bovine serum albumin preparation AMB_2 not included.

pyrogenic, characterized by chills and fever. The reactions were classified as mild moderate, and severe. In the anaphylactoid group, the mild reactions exhibited urticaria alone, the moderate reactions, dyspnea, cyanosis, and urticaria, and the severe reactions, a shocklike fall in blood pressure. In the pyrogenic group, the mild reactions were characterized by slight chills and fever ranging up to 100° F., the moderate reactions by chills of moderate severity and fever not exceeding 103° F., and the severe reactions by severe chills and a temperature over 103° F. On this basis (Table II) there were two mild, five moderate, and one severe reaction. The latter was probably not due to the bovine albumin, for a sporeformer was cultured from the fluids administered, indicating contamination of the solution or rubber tubing.

TABLE II. SEVERITY OF IMMEDIATE AND DELAYED REACTIONS

	IMMEDIATE REACTIONS						DELAYED REACTIONS		
	PYROGENIC			ANAPHYLACTOID					
SERIES	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
A	1	4	1*	1	1	0	3	6	0
B	0	0	0	0	0	0	1	5	1
C	0	0	3†	0	0	0‡	4	15§	1
D	0	0	0	1	0	0	1	1	0
Total	1	4	4	2	1	0	9	27	2

*Sporeform cultured from fluids.

†Probably due to pyrogens in diluents or rubber tubing.

‡One severe anaphylactoid reaction followed the injection of bovine serum albumin preparation AMB_1 not included.

§An additional two delayed reactions of moderate severity followed the injection of bovine serum albumin preparation AMB_2.

The delayed reactions began usually between fourteen and twenty-one days after injection and were characterized by arthralgia, myalgia, and urticaria. The patients with more severe reactions had, in addition, vomiting, diarrhea, and generalized petechial rash. In this series, three mild and six moderately severe reactions were noted (Table II). There were no severe reactions. The incidence and type of reaction with each of the bovine serum albumin preparation utilized are given in Table III. Skin tests were positive in six individuals (7.3 per cent of the patients injected) as indicated by the presence of erythema

TABLE III. INCIDENCE OF REACTIONS, SERIES A

PREPARATION	NO. OF PATIENTS INJECTED	NO. OF INJECTIONS	IMMEDIATE REACTIONS		PATIENTS INJECTED		DELAYED REACTIONS OF PATIENTS INJECTED	
			PYROGENIC	ANAPHYLACTOID	TOTAL NO.	PERCENTAGE	TOTAL NO.	PERCENTAGE
$Alb._{20}$	7	7	0	1	1	14.2	2	28.4
CB_3	3	3	1	0	1	33.3	0	0.0
CB_5	4	4	0	0	0	0.0	0	0.0
CB_7	6	6	0	0	0	0.0	1	16.6
ACB_1	4	5	0	0	0	0.0	0	0.0
ACB_2	7	9	4	0	4	57.1	2	28.6
ACB_3	22	25	1	0	1	4.6	1	4.6
ACB_4	2	7	0	0	0	0.0	0	0.0
ACB_5	18	43	1	0	1	5.5	3	16.6
ACB_7	7	24	0	0	0	0.0	0	0.0
CB_{25}	2	2	0	0	0	0.0	0	0.0
Total	82	135	7	1	8	9.7	9	10.8

and wheal formation. In an additional four the test was equivocal for erythema without wheal formation occurring at the test site. Of the six patients with positive skin tests, five were injected with bovine serum albumin solutions without reactions. Of the six patients developing pyrogenic reactions, one patient had a positive skin test. Of the two patients who developed immediate anaphylactoid reactions, one had a negative skin test and the other had a questionable positive test in that only erythema occurred at the skin injection site. In view of this poor correlation between the negativity and positivity of the skin test with the subsequent development or failure to develop immediate reactions, it was felt that skin testing was of little help in determining likely reactors.

In this series, forty-four patients received more than one injection. Thirty-four patients received two injections, five patients received three injections, one patient received four injections, and one patient received six injections. The time interval between injections varied from twenty-four hours to approximately eighteen months. In all but six the time interval, however, exceeded twenty-seven days. There were no immediate reactions on repeated injections and only four delayed reactions (8.1 per cent). Of these four, one patient had a second injection, ten days following the first, the remaining three had the second injection at 78, 314, and 81 days, respectively, following the original injection.

Ten patients had received bovine plasma from one to two years previously and six had developed both immediate and delayed reactions. However, not one of these patients developed either immediate or delayed reactions subsequent to the injection of crystallized bovine serum albumin solutions.

Series B (April, 1943 to July, 1943).—In all, fifty-seven patients received sixty injections with no immediate reactions and seven delayed reactions (12.3 per cent) (Table I). Of the seven reactions, one was mild, five were moderately severe, and one was severe (Table II). The incidence and type of reaction with each of the bovine serum albumin preparation used is given in Table IV.

Skin tests were applied to all patients in this series with the exception of three. All of the skin tests were negative.

*Series C** (September, 1943, to September, 1945).—There were 232 new injections into an equal number of patients with three immediate pyrogenic reactions (1.3 per cent) and twenty delayed reactions (8.6 per cent) (Table I). All of the pyrogenic reactions may have been due to pyrogens within the rubber tubing or our own diluents, for they occurred when there was a large number of similar pyrogenic reactions attending the administration of simple glu-

*In Series C, eight patients received bovine serum albumin solution AMB_1 with one immediate severe anaphylactoid reaction, and an additional twenty-nine patients received bovine serum albumin solution AMB_2 with no immediate reactions but two moderately severe delayed reactions. AMB_1 was prepared by heating bovine plasma Fraction V[19] (approximately 95 per cent albumin) in a solution containing sodium mandelate to selectively denature the globulin followed by a treatment with formaldehyde, but at a lower temperature than that used by Edwards,[36] in order to avoid the excessive aggregation occurring in his procedure. While these globulins detectable by the precipitation test were thus completely destroyed, electrophoretic analysis showed a trace of another component than albumin and this may have caused the immediate anaphylactoid reaction. AMB_2 was prepared by incubating the concentrated neutral solution of crystallized bovine serum albumin at room temperature with 16 mols of formaldehyde per mol of albumin since this was found to be the maximum amount of formaldehyde which by prolonged treatment under these conditions could be stably bound to the protein, that is, not removed by acid protein precipitants such as tungstic acid. Like AMB_1 it contained only very small amounts of aggregated protein. Because these two preparations were chemically very different from crystallized native bovine serum albumin, they have not been included in the statistical analysis of Series C.

TABLE IV. INCIDENCE OF REACTIONS, SERIES B

PREPARATION	NO. OF PATIENTS INJECTED	NO. OF INJECTIONS	IMMEDIATE REACTIONS		PATIENTS INJECTED		DELAYED REACTIONS OF PATIENTS INJECTED	
			PYROGENIC	ANAPHYLACTOID	TOTAL NO.	PERCENTAGE	TOTAL NO.	PERCENTAGE
CB_{28}	25	26	0	0	0	0.0	1	4.0
ACB_{29}	28	30	0	0	0	0.0	5	17.9
ACB_{30}	4	4	0	0	0	0.0	1	2.5
Total	57	60	0	0	0	0.0	7	12.3

cose and saline solutions. If these were excluded, the over-all incidence of immediate reactions would thus have been 0 per cent.

Table II indicates that the majority of delayed reactions were of either mild or moderate severity. In only one instance was the reaction particularly severe. Table V lists the incidence and type of reaction with each of the bovine serum albumin preparations used.

TABLE V. INCIDENCE OF REACTION, SERIES C

PREPARATION	NO. OF PATIENTS INJECTED	IMMEDIATE REACTIONS		PATIENTS INJECTED		DELAYED REACTIONS OF PATIENTS INJECTED	
		PYROGENIC	ANAPHYLACTOID	TOTAL NO.	PERCENTAGE	TOTAL NO.	PERCENTAGE
$ACB_{32}H_1$	16	0	0	0	0.0	1	6.3
ACB_{33}	59	3	0	3X	5.1	5	8.5
$ACB_{33}H_2$	8	0	0	0	0.0	1	12.5
ACB_{35}	15	0	0	0	0.0	0	0.0
ACB_{36}	12	0	0	0	0.0	1	8.3
ACB_{37}	25	0	0	0	0.0	2	8.0
ACB_{41}	58	0	0	0	0.0	3	5 2
ACB_{44}	32	0	0	0	0.0	4	12.2
ACB_{47}	7	0	0	0	0.0	3	42.8
Total	232	3	0	3	1.3	20	8.6

X, Probably due to pyrogens within the rubber tubing or diluents.

Series D (Reinjection series September, 1944, to September, 1945).—Thirty-nine patients received 42 injections with one immediate reaction (2.6 per cent) and two delayed reactions (5.2 per cent) (Table I). The time interval between injections varied from 10 to 807 days.

TABLE VI. INCIDENCE OF REACTIONS, SERIES D

PREPARATION	NO. OF PATIENTS INJECTED	NO. OF INJECTIONS	IMMEDIATE REACTIONS		PATIENTS INJECTED		DELAYED REACTIONS OF PATIENTS INJECTED	
			PYROGENIC	ANAPHYLACTOID	TOTAL NO.	PERCENTAGE	TOTAL NO.	PERCENTAGE
ACB_{33}	18	18	0	0	0	0.0	1	5.6
ACB_{36}	7	7	0	0	0	0.0	0	0.0
ACB_{37}	5	5	0	0	0	0.0	0	0.0
ACB_{41}	9	12	0	1	1	11.1	1	11.1
Total	39	42	0	1	1	2.6	2	5.2

The immediate reaction was of mild severity and occurred in a patient (V. B., U. H. No. 730470) who had developed delayed reactions to two previous injections of bovine serum albumin preparations.

Of the delayed reactions, one was mild and one of moderate severity (Table II). Both of the patients had developed serum sickness on previous injections of bovine serum albumin solutions. The incidence and type of reaction with each of the bovine serum albumin preparations injected are given in Table VI.

That a previous reaction either immediate or delayed, following the injection of bovine serum albumin, is not always repeated on subsequent injection is evidenced by the circumstance that two patients who had had immediate reactions and three patients who had delayed serum sickness following previous injections, on this occasion did not experience further difficulty when injected.

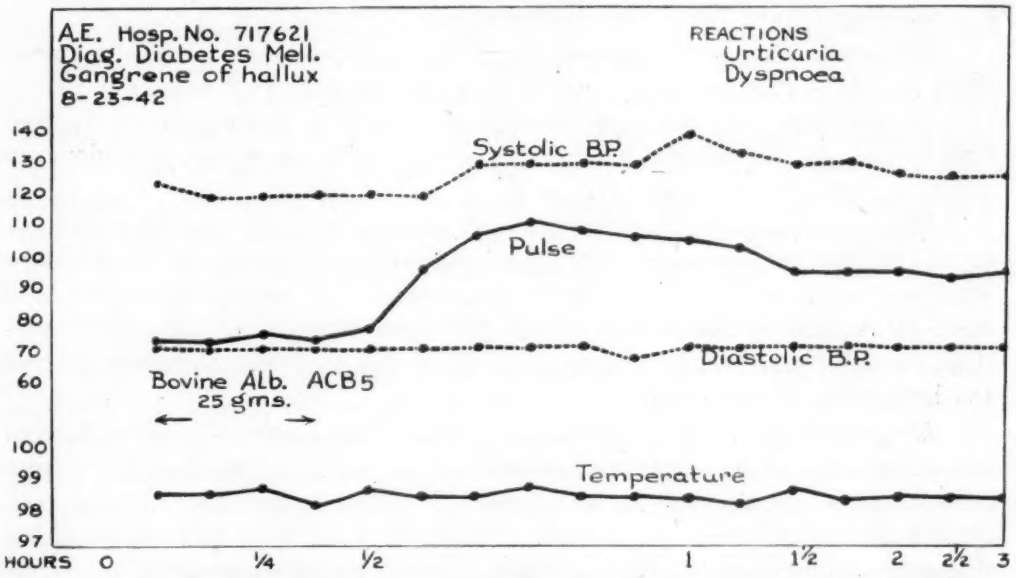

Fig. 1.—Pyrogenic reaction following the administration of bovine serum albumin preparation ACB_5.

A typical example of a moderately severe immediate reaction seen in the study is that of A. E., U. H. No. 717621, No. 40 Series A, a white, 62-year-old man, with diabetic gangrene of the left great toe who received 25 Gm. of bovine serum albumin preparation ACB_5 in ten minutes on Aug. 23, 1942. He then developed urticaria, dyspnea, hoarseness, and edema of the eyelids. There was a moderate elevation of the pulse rate but no change in temperature, respiration, and blood pressure (Fig. 1). The manifestations were readily controlled by the administration of 0.5 c.c. of $\frac{1}{1000}$ adrenalin hydrochloride subcutaneously.

The most severe delayed reaction occurred in the instance of M. E., U. H. No. 740179, No. 38 Series C, a white 19-year-old man, who was admitted to the hospital for a traumatic laceration of the right ulnar and median nerves. On May 18, 1944, he received 25 Gm. of bovine serum albumin preparation ACB_{36} without reaction. On May 30, 1944 (twelve days later), he noted headache,

anorexia, and cervical adenopathy. On the following day, he developed arthralgia, myalgia, chills, fever, and maculopapular rash on the feet and legs. On June 5, 1944, he developed a purpuric rash over the back and a bloody diarrhea. Blood pressure fell from 100/90 mm. Hg to 86/60 and he was given 500 c.c. of whole blood with elevation of the blood pressure to 110/70 mm. Hg. The general condition remained unchanged until June 11, 1944, when all signs and symptoms apart from arthralgia and a low grade fever subsided.

He was given 1 Gm. of procaine in 500 c.c. of saline solution intravenously on June 14, 1944, with prompt disappearance of the fever and subsidence of the arthralgia. This response to procaine led to its use in all subsequent cases of delayed serum sickness with excellent results.[18] It is quite possible that if we had used it earlier in this patient the severity and duration of the serum sickness might have been lessened materially.

Summary.—In all, 410 patients received 469 injections with twelve immediate reactions (2.9 per cent) and 38 delayed reactions (9.2 per cent) (Table I). Of the immediate reactions, three were mild, five moderately severe, and four severe. Of the delayed reactions, nine were mild, twenty-seven moderately severe and two severe (Table II).

When one compares the incidence and severity of both immediate and delayed reactions in this study with those published by Kremen and associates[5, 6] with bovine plasma it can readily be appreciated that real progress has been made by separating out and purifying the albumin fraction; immediate reactions virtually have been eliminated and the incidence of delayed serum sickness has been reduced considerably.

At present, bovine serum albumin solutions can be given with no fear of immediate reaction beyond the incidence rate of reaction attending the administration of whole blood.[19] It is only fair to add however, that delayed antigenic reactions of bovine serum albumin are somewhat more disturbing. Also, the severe anaphylactoid reactions that followed the administration of bovine serum, plasma, and the earlier albumin fractions separated by precipitation with ammonium sulfate have been eliminated entirely in the later preparations of Cohn and Hughes, Jr. One further point of interest and great practical importance is that the incidence of immediate reactions is no greater in the reinjection series than in the initial injection series.

The incidence of immediate reactions in Series B, C, and D can be considered to be 0 per cent approximately. As explained previously, three of the reactions in Series C might well have been due to contamination of the rubber tubing or our own diluents, for they occurred at a time when many reactions appeared throughout the hospital, even following the administration of glucose and saline solutions.

In contrast to this marked and progressive decrease in the incidence of immediate reactions there has not been a continual decrease in the incidence of delayed reactions. Following the marked initial drop attending the utilization of the purified albumin fraction, as contrasted to whole bovine plasma and serum, the percentage of delayed reactions has remained fairly constant at 5 to

10 per cent in all of the series. It should again be emphasized that the incidence of delayed reactions in the reinjection series is no higher than in the initial injection series.

Two major problems therefore present themselves. First, the elimination of the delayed reactions and, second, the detection of possible reactors.

The elimination of delayed reactions by still further purification of bovine serum albumin seems hardly likely, for some of the bovine serum albumin preparations supplied to us by Cohn and Hughes, Jr., have had as little as .005 Gm. per cent of globulin and yet delayed reactions attended their use. Despeciation according to the method of Edwards[16] also has failed to eliminate both immediate and delayed reactions. It is to be hoped that someone will come forward with a plan which will eliminate the antigenic factor in bovine serum albumin.

The methods used to detect possible reactors have consisted of skin testing and close questioning of the individuals for allergies prior to the administration of bovine serum albumin. Both of these methods have been unsuccessful. Delayed reactions occurred frequently in the absence of a positive skin test and despite a negative history of hypersensitivity. Conversely, patients with a positive skin test or history of allergy did not develop either immediate or delayed reactions. However, it should be noted that no strongly positive skin tests were encountered and it is possible that only very strongly positive skin tests (wide flare, large wheal, itching, and pseudopods) have real significance.[20]

INTRAVENOUS PROCAINE ABORTS SERUM SICKNESS

Procaine given intravenously was an extremely effective antidote for serum sickness.[18] Sixteen patients with delayed serum sickness were given 2 Gm. of procaine diluted to 500 c.c. with normal saline over a period of two hours. Ten individuals obtained immediate and complete relief after one or more injections. An additional four obtained only temporary or partial relief and two were not benefited at all.

Its exact mode of action is not clear but the following hypotheses have been postulated: (a) direct action on the cells, (b) antihistamine action, (c) anti-acetylcholin action, and (d) adrenalin-potentiating action.

PERIARTERITIS NODOSA AND PANCARDITIS NOT OBSERVED

Bailey and Hawn[21] have been able to demonstrate the presence of periarteritis nodosa and pancarditis in rabbits sensitized to bovine serum albumin. In this study it was possible to check the post-mortem findings in seven patients who had received bovine serum albumin, but had died of other causes. Two of these patients had had serum sickness. The time interval between the last injection of bovine serum albumin and the autopsy varied from two days to eighteen months in these patients. There was no pancarditis and in no instance were evidences of periarteritis nodosa observed, either grossly or microscopically in the following organs: brain, lungs, skin, spleen, heart, esophagus, stomach, duodenum, small and large bowels, liver, pleura, kidneys, gall bladder, urinary bladder, prostate, testes, ovary, uterus, Fallopian tubes, aorta, vertebrae, adrenals, psoas muscle, and diaphragm.

EFFICACY OF BOVINE SERUM ALBUMIN SOLUTIONS AS A BLOOD SUBSTITUTE

Since most of the surgery in the surgical division of the University Hospitals is of an elective nature, few cases were available to study the effectiveness of bovine serum albumin solutions in the treatment of shock. In the earlier phases of the work, three patients who were in shock were available and were studied. Two patients who underwent major surgical procedures and to whom bovine serum albumin was given to determine its value in the prevention of the onset of shock were studied. As this investigation progressed it became apparent that the prime phase of importance was to determine the safety of administration of bovine serum albumin solutions and it was felt that multiple large injections of bovine serum albumin solutions should not be given until more definite data on its relative safety in administration were available. Because of this, the study of the efficacy of bovine serum albumin in prevention and treatment of shock was not pursued.

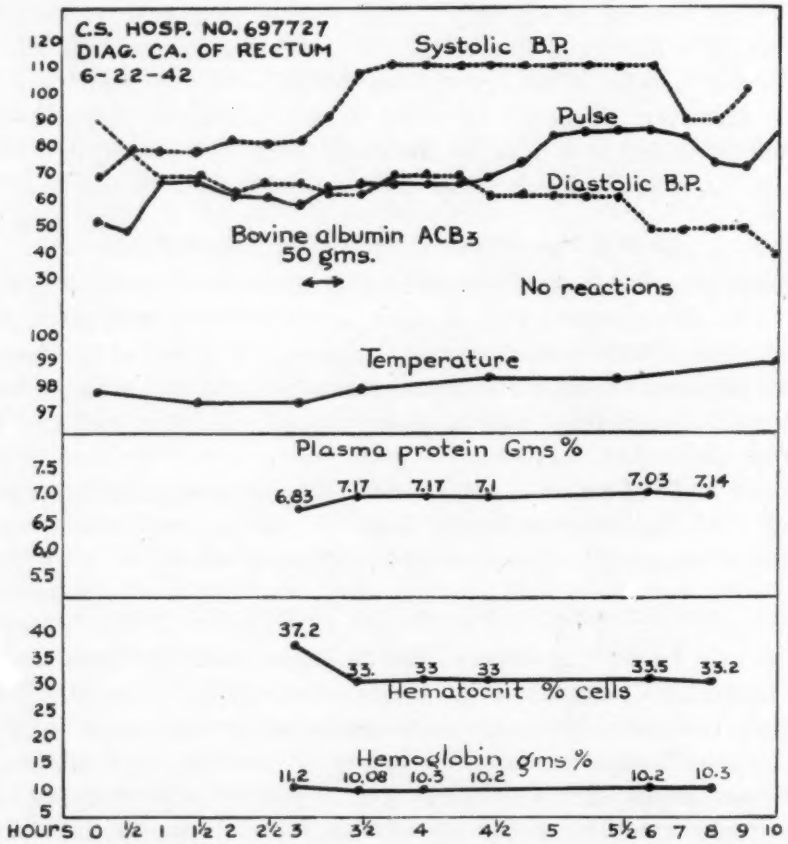

Fig. 2.—Efficacy of bovine serum albumin in the treatment of shock.

BOVINE SERUM ALBUMIN SOLUTIONS IN THE TREATMENT OF SHOCK

CASE 1 (U. H. No. 697727).—C. S., a white man, was 64 years of age. Diagnosis of carcinoma of the rectum with extensive metastases was made. On June 22, 1942, he had bilateral cervical chordotomy for intractable pain secondary to metastases to the lumbar

spine and pelvis. The operation lasted from 3:30 to 5:30 P.M. Although the blood loss was not measured, it was thought not to be excessive. The blood pressure at the start of the operation was 158/74 mm. Hg and the pulse 76 per minute. Toward the end of the operation the blood pressure fell to 90/60 mm. Hg and the pulse was 82 per minute. During the operative procedure he received 1,000 c.c. of normal saline solution intravenously. For the first four hours after surgery the blood pressure ranged between 78/52 and 84/60 mm. Hg and the pulse between 72 and 90 per minute. During this period he received 1,000 c.c. of 5 per cent glucose in normal saline solution intravenously and 1,000 c.c. of 5 per cent glucose in distilled water subcutaneously without appreciable effect on blood pressure or pulse rate. At 9:35 P.M. (approximately four hours after completion of the operation) he was given 50 Gm. of bovine serum albumin solution ACB_3 diluted to 300 c.c. with normal saline solution in twenty minutes. The blood pressure began to rise almost immediately. At 10 P.M., it was 110/64 mm. Hg, and it remained at about this level until 3 A.M., when observations were discontinued. Although there was little change in the pulse rate, there was a definite improvement in its quality. The hemoglobin (Sahli), hematocrit (Wintrobe tube 3,000 revolutions per minute for thirty minutes), and plasma proteins were taken immediately before the administration of the bovine serum albumin solution and at one-half and hourly intervals thereafter. Definite evidence of rather marked hemodilution was noted following the use of the bovine serum albumin solution (Fig. 2).

CASE 2 (U. H. No. 673124).—R. T., a white man, was 48 years of age. Diagnosis of chronic osteomyelitis of the left tibia was made. On March 3, 1942, he had a skin flap applied over a cutaneous sinus, secondary to chronic osteomyelitis of the left tibia. There was considerable bleeding (amount, however, was not measured) and the operation lasted three hours and fifteen minutes. During the first hour of operation, the blood pressure was consistently 170/90 mm. Hg and the pulse 96 per minute. During the second hour of operation, the blood pressure fell to 140/70 mm. Hg, and the pulse rose to 110 per minute. He was then given 500 c.c. whole blood with no change in blood pressure or pulse. In addition to the blood the patient received 500 c.c. normal saline solution intravenously during the operation. On returning to his bed in the surgical ward, the patient's blood pressure fell to 60/14 mm. Hg and the pulse rose to 118 per minute. He was placed in steep Trendelenburg position but no parenteral fluids were given. During the next forty minutes the blood pressure rose gradually to 80/50 mm. Hg, but the pulse remained between 100 and 110 per minute. He was then given 100 c.c. of bovine serum albumin solution CB_6 (25 Gm.) undiluted over a period of fifteen minutes. Five minutes after the albumin solution had run in, the blood pressure rose to 100/60 mm. Hg and the pulse slowed to 90 per minute. The blood pressure then was maintained adequately between 100/60 to 140/60 mm. Hg until the patient regained full consciousness in two and one-half hours. In this same interval the patient also received 500 c.c. of 5 per cent glucose in normal saline solution intravenously. Unfortunately, hemoglobin, hematocrit, and plasma protein values were not obtained.

CASE 3 (U. H. No. 723323).—M. K., a white woman, was 23 years of age. Diagnosis of compound fracture of the right tibia and lacerated tendons of the right leg was made. This patient was injured on Aug. 17, 1942, approximately two hours before coming into the hospital. On admission, she was in acute pain and the skin was cold, moist, and pale. A tourniquet had been in place around the right leg for approximately one hour. The blood pressure, pulse, and respiration were respectively 132/70 mm. Hg, 90, and 24 per minute. Prior to surgery, she was given 100 c.c. (25 Gm.) of bovine serum albumin solution ACB_3 diluted to 200 c.c. with normal saline solution and during the operation for reduction of the fracture and repair of the tendons she was given an additional 25 Gm. In addition, she received 500 c.c. normal saline solution during surgery. The operation lasted two hours and fifteen minutes and apart from a temporary fall of blood pressure subsequent to the release of the tourniquet the blood pressure was uniformly maintained between 120/70 and 130/70 throughout and following the surgical procedure. The accompanying chart (Fig. 3) also shows the fall in hemoglobin and hematocrit values indicating definite hemodilution.

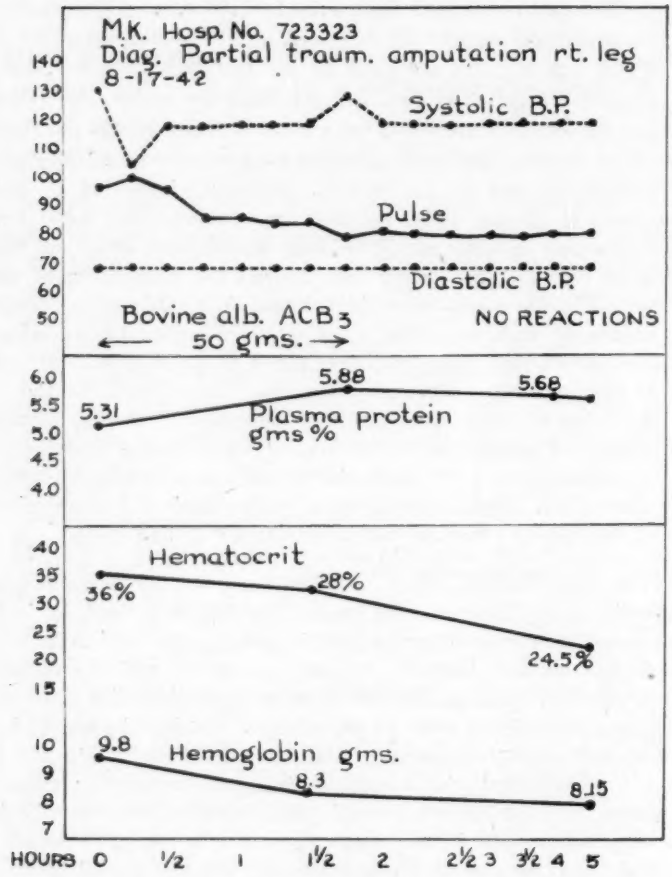

Fig. 3.—Efficacy of bovine serum albumin in the treatment of shock.

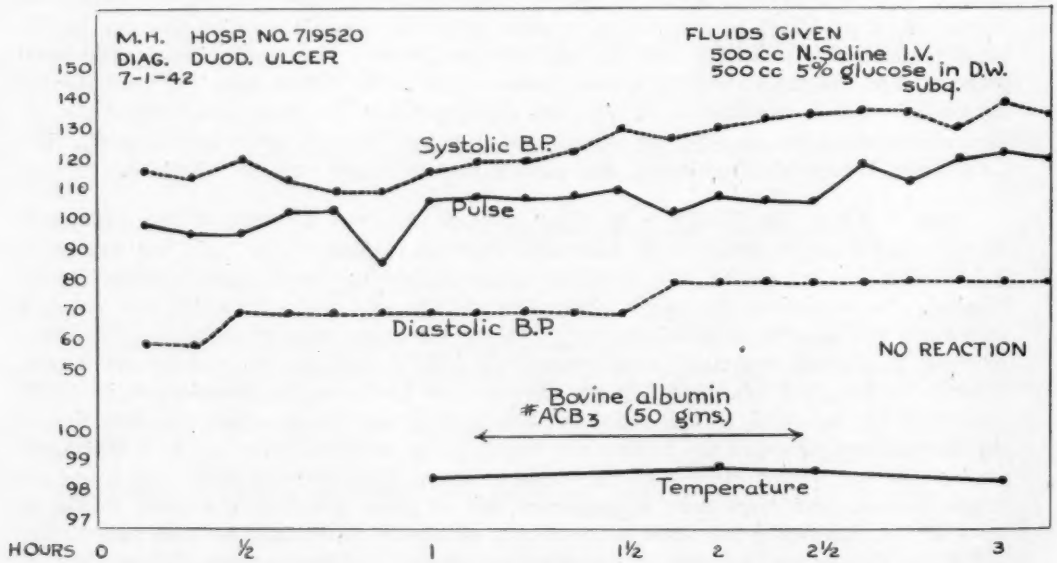

Fig. 4.—Efficacy of bovine serum albumin in the prevention of the onset of shock.

BOVINE SERUM ALBUMIN SOLUTION IN THE PREVENTION OF THE ONSET OF SURGICAL SHOCK

CASE 1 (U. H. No. 719520).—M. H., a white man, was 44 years of age. Diagnosis of duodenal ulcer was made. On July 1, 1942, a partial gastrectomy for duodenal ulcer was done. The duration of the operation was three hours and forty minutes. Blood pressure, pulse, and respiration before the operation were, respectively, 118/60 mm. Hg, 100, and 20. At the completion of the surgical procedure they were, respectively, 136/80 mm. Hg, 100, and 22, and as can be seen from the chart they were well and uniformly maintained throughout the operation (Fig. 4). The blood loss during operation (as determined by measuring the increment in gain of dry sponges[22]) was 528 Gm. In addition to 50 Gm. of bovine serum albumin ACB_3 the patient received 500 c.c. of normal saline solution intravenously and 500 c.c. of 5 per cent glucose in distilled water subcutaneously.

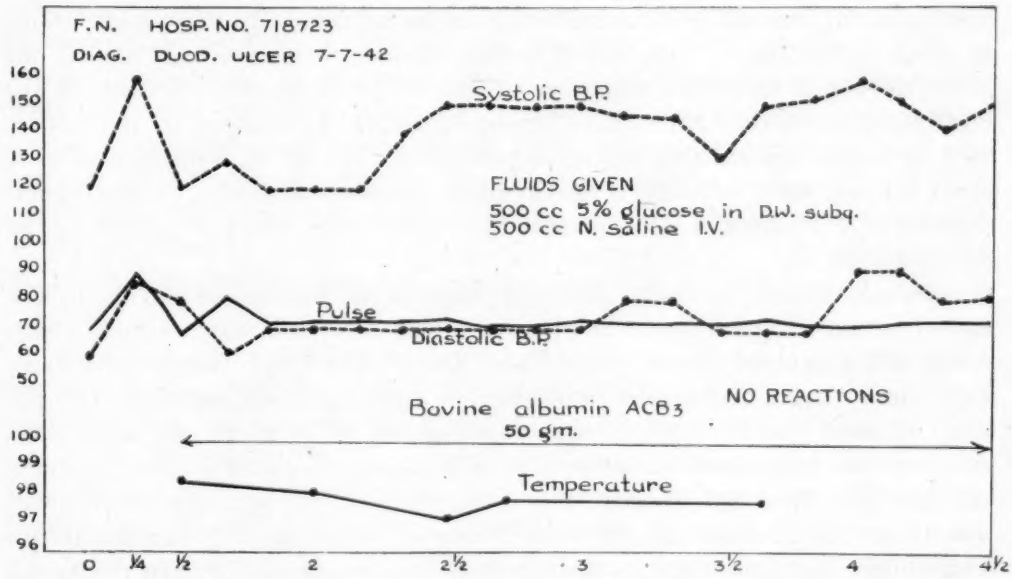

Fig. 5.—Efficacy of bovine serum albumin in the prevention of the onset of shock.

CASE 2 (U. H. No. 718723).—F. N., a white man, was 62 years of age. Diagnosis of duodenal ulcer was made. A partial gastrectomy for duodenal ulcer was done on July 7, 1942. The duration of the operation was three hours and forty-five minutes. The blood pressure and pulse prior to surgery were, respectively, 120/60 mm. Hg and 70 per minute. Throughout operation these were well maintained and at the completion of the operation the blood pressure and pulse were, respectively, 150/80 mm. Hg and 74 per minute. He received 50 Gm. of bovine serum albumin ACB_3 diluted with 500 c.c. of 5 per cent glucose in distilled water and 500 c.c. of normal saline solution intravenously. The blood loss during surgery was 512 Gm. (Fig. 5).

Discussion.—Surgeons have long known that blood is the best agent with which to combat large blood losses. The surgical experience of World War II has lent greater emphasis to this knowledge. In the main, fluid losses sustained by patients are best replaced in kind and in the amount of the loss with a minimal lag interval. The use of dry sponges by surgeons during operation and ascertainment of their accretion in weight[22] serves to keep the surgeon informed throughout the operation concerning the extent of the blood loss. For blood losses of 800 c.c. or less the administration of plasma in our experience meets

the demands of the situation satisfactorily. The all too limited experience with bovine serum albumin in the management of shock detailed in the cases cited suggests moreover that, with development of a nonantigenic bovine albumin, this agent may prove useful in the management of the less serious forms of hematogenic shock.

Of the three cases of shock available for study, two were immediately postoperative and the other followed an extensive injury. In the former two cases, the operative trauma and inadequate blood loss replacement were probably primarily responsible for the development of shock. In the last case although the blood pressure was not low, the other clinical manifestations of shock were present and, in addition, a tourniquet which had been applied for one hour had to be removed in order to repair the injured extremity. As Bayliss and Cannon[23] showed, removal of a tourniquet from an injured extremity might result in shock. Mindful of this, bovine serum albumin was given to combat the minor degree of shock on admission as well as preventing an increase in the severity of shock that might have arisen following the removal of the tourniquet or during the ensuing operative procedure. As can be seen from Fig. 3, apart from a very temporary fall in blood pressure after the release of the tourniquet, the patient's blood pressure and pulse were well maintained during the operation.

On physiologic grounds, albumin, whether of human or bovine origin, should be an effective agent in drawing fluid from the extracellular tissue spaces into the blood stream. Stead and Ebert[27] and Heyl, Gibson, and Janeway[28] have shown that concentrated bovine serum albumin solutions (25 per cent) injected into normal subjects after removal of 10 to 20 per cent of the blood volume by venesection is capable of restoring the blood volume by drawing fluid into the blood stream. The latter group of investigators also showed that there was no essential difference between human and crystallized bovine serum albumins in their ability to draw fluid into the circulation. In this study, it can be seen in two of the cases of shock in which the hemoglobin, hematocrit, and plasma proteins were taken, that there was a marked reduction in the values of the former two, indicating a pronounced degree of hemodilution. There was an increase of the plasma proteins in spite of the hemodilution due probably to the added bovine serum albumin which was retained in the circulatory system. In experimental studies, Dunphy and Gibson[24] have shown that bovine serum albumin is effective in combating burn shock in dogs, and Fine and co-workers[25] have also demonstrated its efficiency in combating tourniquet shock.

Because a marked hemodilution occurs following the use of hyperosmotic bovine serum albumin solutions, these are more effective in dehydrated states when supplemented with adequate amounts of iso-osmotic saline or glucose solutions.

EFFICACY OF BOVINE SERUM ALBUMIN SOLUTION IN THE TREATMENT OF INCREASED INTRACRANIAL PRESSURE

CASE 1 (U. H. No. 737452).—M. R., a white girl, was 6 years of age. This patient had sustained a severe cerebral injury on Nov. 14, 1943, following a fall on her head. She

was brought to the University Hospital on Nov. 15, 1943, in a semiconscious state. Trephine holes were made in the temporal and parietal areas bilaterally to rule out a subdural hematoma, but none was found. Her condition grew worse in spite of attempts to reduce intracranial pressure by means of a concentrated sucrose solution intravenously. On Nov. 16, 1943, she was moribund and as a last attempt to reduce the intracranial pressure, 50 c.c. (12.5 Gm.) of undiluted bovine serum albumin preparation ACB_{32} was given intravenously. Approximately one hour later, a definite improvement in the child's condition was noted. She responded to the spoken voice, smiled, coughed, and expectorated. On Nov. 17, 1943, she was given an additional 8 Gm. of $ACB_{32}H_1$ in 20 c.c. of saline solution with continued improvement so that it was felt that she would make a complete recovery. On Nov. 24, 1943, however, she died quite suddenly and a post-mortem examination revealed the presence of a large occipital subdural hematoma.

Discussion.—Since bovine serum albumin molecules do not readily leave the circulatory system they exert a prolonged osmotic pressure which would cause tissue fluid to pass from the extracellular spaces into the blood stream, thus relieving tissue edema. In contrast to this, a hypertonic solution of either glucose or sucrose would initially draw fluid from the extracellular spaces into the blood stream. But the molecules would soon leave the circulatory system and pass into the extracellular tissue spaces, exerting their osmotic force here, thus tending to draw fluid back from the blood stream into the tissue spaces. Clinically this is paralleled by a temporary reduction in tissue edema followed by a secondary increase which might be greater than the amount present prior to injection.

In all severe head injuries there is some degree of cerebral edema; prolonged reduction of such edema is not possible by means of hypertonic glucose or sucrose solutions, for after the initial decrease in intracerebral pressure there is a marked secondary rise. However, by means of hyperosmotic bovine serum albumin solutions, a more marked and prolonged influence on intracerebral pressure is to be expected on physiologic grounds.

In confirmation of this is the marked clinical improvement of the patient just described. Hypertonic sucrose solution had been used with only slight and temporary improvement and the bovine serum albumin solution was used only as a terminal gesture, for it was felt that the patient could not recover.

Unfortunately, the subdural hematoma was at a very unusual spot for if trephining and discovery of it could have been done after the improvement of the patient occurred, it is not unreasonable to assume that the patient might have made a recovery.

SUMMARY AND CONCLUSIONS

Using highly purified bovine serum albumin fractions obtained by precipitation of bovine plasma by ethanol alcohol at -5° C., 469 injections have been made into 410 patients with twelve (2.9 per cent) immediate reactions and thirty-eight (9.2 per cent) delayed reactions. Using bovine plasma and serum, Kremen and associates[5, 6] noticed an incidence of approximately 50 per cent immediate reactions and 60 per cent delayed reactions. There has thus been a marked reduction in the incidence of immediate and delayed reactions attending the use of purified bovine serum albumin fractions.

Immediate reactions were of two types: (1) anaphylactoid, characterized by dyspnea, cyanosis, and fall in blood pressure (2) pyrogenic, characterized by chills and fever. In the main, the reactions were moderately severe.

The onset of the delayed reactions was usually from twelve to twenty-four days after injection and was characterized by urticaria, erythema, myalgia, arthralgia, and fever. In the severe cases, there were petechiae and ecchymoses.

The incidence of both immediate and delayed reactions was no greater in patients who received multiple injections than in those receiving a single injection.

Skin testing is not an effective means of determining the sensitivity of patients to bovine serum albumin.

Despeciating both purified and crystallized bovine serum albumin with a modification of the method of Edwards[16] has not eliminated immediate or delayed reactions.

Procaine given intravenously (1 Gm. in 200 c.c. saline solution over an interval of one hour) is a very effective agent in the treatment of delayed serum sickness.

No evidences of periarteritis nodosa or pancarditis were noted in the postmortem findings of seven patients who had received bovine serum albumin but who died of other causes.

In concentrated solutions (25 per cent) bovine serum albumin would appear to be an effective agent in the prevention and treatment of shock. For large blood loss, in excess of 800 c.c., blood obviously would be a more satisfactory agent with which to combat shock.

In dehydrated states, isotonic saline and glucose solutions should be given along with the hyperosmotic bovine serum albumin solutions.

In the one instance available for study, hyperosmotic bovine serum albumin solution (25 Gm. per cent) was apparently effective in combating cerebral edema.

Because of the persistence of, and incapacity caused by, the delayed reactions, crystallized bovine serum albumin is not recommended at present as an ideal blood substitute. New methods of despeciation may eliminate the antigenicity of bovine serum albumin.

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CHANGES IN PLASMA VOLUME AND MEAN ARTERIAL PRESSURE AFTER THE INTRAVENOUS INJECTION OF CONCENTRATED HUMAN SERUM ALBUMIN IN THIRTY-EIGHT PATIENTS WITH OLIGEMIA AND HYPOTENSION

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WITHIN the past three years, clinical studies on the intravenous use of concentrated human serum albumin for the treatment of shock and shock-like conditions have been undertaken by several groups of investigators.[1-4] The purpose of these studies was to determine the efficacy of this agent in assisting recovery from shock. The present report is concerned primarily with a comparison of the effects upon mean arterial blood pressure and plasma volume of the intravenous injection of concentrated human albumin solutions when given with and without additional intravenous fluids. In a number of instances, the effects of a new salt-poor albumin preparation have been compared with those obtained with the standard albumin solution containing 0.3 M.NaCl.

The results of this study are presented as follows: First the data are given on 20 patients each of whom received varying amounts of concentrated human albumin without additional intravenous fluids. Of these, 7 received the salt-poor preparation, 13 the standard product. Second, the data on 18 patients are given, each of whom received varying amounts of concentrated human albumin *with* additional intravenous fluids, usually in the form of normal saline solution. Six patients in this group were given the salt-poor albumin, 12 the standard solution.

MATERIAL AND METHODS

Varous clinical conditions were studied, namely, postoperative states (extensive resections of the chest wall, resections of the lung, and various types of abdominal surgery), injuries, burns, and acute abdominal conditions. These included patients with and without shock.

Two different solutions of concentrated (25 per cent) human serum albumin were administered: the standard albumin solution containing 0.3 M.NaCl and the newer, salt-poor albumin preparation containing 0.04 M.Na mandelate or 0.04 M.Na acetyl tryptophane.

The techniques employed in this study are described in the previous article.[5] In each patient, plasma volume, hematocrit, serum protein concentration, and mean arterial blood pressure were measured before and at suitable intervals after

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injection of the concentrated albumin solution. From these determinations, the following data were calculated: (1) Total circulating protein, (2) total circulating albumin, (3) plasma volume increase per gram of albumin injected, and (4) plasma volume increase per gram of albumin retained.

Plasma volume was measured before and at suitable intervals after injection of the albumin by the dye dilution method with T-1824. Determination of total plasma volume was made from one arterial blood sample obtained ten minutes after the intravenous injection of the blue dye. In cases of severe shock, three additional blood samples were withdrawn at successive ten-minute intervals to insure a more exact measurement of the plasma volume.[6] Hematocrits were determined by the method of Wintrobe. In calculating plasma volume changes, account was taken of the blood removed for sampling between successive plasma volume measurements. Serum protein concentrations (Howe method) were determined on blood samples obtained at the time of each plasma volume measurement. The total circulating protein and the total circulating albumin were calculated as the product of plasma volume times the serum protein and the serum albumin concentrations, respectively. Protein loss due to sampling between determinations was calculated according to a method described elsewhere.[7] The plasma volume change per gram of albumin injected was then calculated from the total plasma volume increase in cubic centimeters divided by the total amount of albumin injected in grams. Similarly, the plasma volume change per gram of albumin retained was computed from the total plasma volume increase in cubic centimeters divided by the increase in total circulating albumin in grams.

RESULTS

The Effect of the Intravenous Injection of Concentrated Human Serum Albumin Upon Plasma Volume, Hematocrit, and Serum Proteins When Given Without Additional Crystalloid Solution.—Table I shows the data derived from the study of twenty patients each of whom received concentrated human albumin intravenously without additional intravenous fluids. In Column 1, the patient's initials are given together with the clinical diagnosis. In Column 2, note is made of the time elapsing between the end of the albumin injection and subsequent measurements. The letters "N" and "D" listed in Column 3 denote the fluid state of the patient (whether normal or dehydrated) at the time of the initial study, as judged by the history and general clinical appearance of the patient. Column 4 indicates the type of albumin preparation used, and the amount injected in grams.

The values for mean arterial blood pressure, total plasma volume, and hematocrit are given in Columns 6, 7, and 8, respectively. In the next four columns (9, 10, 11, and 12), the serum protein values in grams per cent and the total circulating protein in grams are given.

The distribution of the twenty patients listed in Table I is as follows:

15 postoperative cases (lung and chest wall resections—abdominal surgery)

1 case of marked dehydration due to pyloric obstruction

TABLE I. PLASMA VOLUME AND PLASMA PROTEIN CHANGES FOLLOWING INJECTION OF CONCENTRATED HUMAN ALBUMIN

PATIENT AND DIAGNOSIS	TIME	FLUID STATE*	ALBUMIN INJECTED (GM.)†	FLUID WITH ALBUMIN (C.C.)	MEAN ART. B.P. (MM.)	PLASMA VOL. (C.C.)	HEMATOCRIT %	PLASMA PROTEIN ALBUMIN %	PLASMA PROTEIN GLOBULIN %	PLASMA PROTEIN TOTAL %	PLASMA PROTEIN TOTAL (GM.)	PLASMA VOLUME CHANGE PER GM. ALBUMIN INJECTED	PLASMA VOLUME CHANGE PER GM. ALBUMIN RETAINED
1. Y. C., P.O. thoracoplasty	ā	N	–	–	55	2410	40	3.4	2.5	5.9	142	–	–
	7 m. p̄		24 (S-P)	–	78	2950	36	3.5	2.6	6.1	180	23	26
2. K. C., P.O. thoracoplasty	ā	N	–	–	42	1988	38	3.9	2.8	6.7	135	–	–
	16 m. p̄		48 (S-P)	–	50	2240	32	5.0	2.4	7.4	166	5	8
3. J. P., P.O. thoracoplasty	ā	N	–	–	54	1855	39	3.7	2.9	6.6	123	–	–
	15 m. p̄		49	–	76	2900	28	4.8	2.2	7.0	203	21	15
4. J. O., P.O. lobectomy	ā	N	–	–	72	2240	41	4.5	2.1	6.6	148	–	–
	23 m. p̄		49	–	80	2980	37	5.1	1.7	6.8	202	.15	15
5. L. Z., P.O. thoracoplasty	ā	N	–	–	54	2532	35	3.5	2.6	6.1	155	–	–
	15 m. p̄		49	–	62	3895	29	4.4	2.1	6.5	208	28	26
6. H. E., acute pancreatitis	ā	N	–	–	61	2290	41	2.9	2.0	4.9	112	–	–
	10 m. p̄		64	–	62	2975	36	4.1	1.7	5.8	172	11	13
	2 h., 30 m p̄		–	–	60	2975	35	3.8	1.7	5.5	163	11	16
7. S. J., P.O. lobectomy	ā	N	–	–	60	2420	36	4.3	2.8	7.1	172	–	–
	12 m. p̄		48	–	83	2910	33	4.9	2.4	7.3	212	10	13
8. X. L., P.O. strangulated hernia	ā	N	–	–	38	2520	43	2.6	1.7	4.3	109	–	–
	18 m. p̄		75	–	62	3305	36	4.3	1.1	5.4	178	10	11
	2 h., 19 m. p̄		–	–	48	2902	38	4.1	1.2	5.3	154	5	7
9. C. B., Traumatic lacerations, alcoholism	ā	N	–	–	61	3210	42	3.8	2.0	5.8	177	–	–
	55 m. p̄		25 (S-P)	–	72	3400	38	4.2	2.0	6.2	210	8	8
10. S. H., P.O. gastric ulcer	ā	N	–	–	78	1600	39	3.4	2.1	5.5	89	–	–
	13 m. p̄		36 (S-P)	–	117	1875	31	5.4	1.4	6.8	127	8	6
	3 h. p̄		–	–	123	2150	29	4.8	1.4	6.2	133	15	12

11. K. C., P.O. thoracoplasty	ā	N	–	–	52	2440	35	3.4	3.3	6.7	164	–	–
	21 m. p̄		50 (S-P)	–	70	3230	25	4.8	2.3	7.1	299	16	11
	3 h. p̄		–	–	77	3120	25	4.6	2.1	6.7	209	14	12
12. Y. C., P.O. thoracoplasty	ā	N	–	–	64	2410	38	2.5	3.7	6.2	150	–	–
	17 m. p̄		30 (S-P)	–	80	3090	36	4.0	2.8	6.8	210	16	11
	3 h. p̄		–	–	81	2586	35	4.1	2.6	6.7	173	6	4
13. J. B., Exposure to cold	ā	N	–	–	59	2810	35	3.5	3.9	7.4	210	–	–
	14 m. p̄		50 (S-P)	–	47	3290	33	4.1	3.7	7.8	257	12	14
14. S. P., P.O. thoracoplasty	ā	N	–	–	58	2236	37	4.0	1.8	5.8	130	–	–
	20 m. p̄		48	–	70	2750	29	4.2	1.8	6.0	166	11	20
	4 h. p̄		–	–	70	3050	29	4.6	1.8	6.4	195	17	16
15. B.S., P.O. thoracoplasty	ā	N	–	–	93	2241	38	3.4	2.8	6.2	139	–	–
	17 m. p̄		25	–	103	2540	35	4.3	2.6	6.9	176	12	9
	2 h., 37 m. p̄		–	–	99	2712	35	4.1	2.6	6.7	180	19	14
16. G. F., P.O. lobectomy	ā	N	–	–	52	2972	38	4.2	2.1	6.3	188	–	–
	31 m. p̄		50	–	88	3240	33	3.5	2.8	6.3	204	5	0
	3 h., 32 m. p̄		–	–	94	3622	35	4.6	1.6	6.2	228	13	12
17. L. V., Mesenteric thrombosis	ā	D	–	–	66	1366	55	2.6	3.2	5.8	80	–	–
	21 m. p̄		47	–	86	1630	50	5.4	1.3	6.7	109	6	6
	2 h. 13 m. p̄		–	–	94	1910	47	4.5	1.4	5.9	113	12	11
18. L. F., Pyloric obstruction	ā	D	–	–	68	2739	30	3.1	1.9	5.0	137	–	–
	1 h. p̄		50	–	75	3168	27	4.1	1.3	5.4	171	9	10
19. H. G., P.O. thoracoplasty	ā	N	–	–	75	2241	32	3.2	1.7	4.9	110	–	–
	17 m. p̄		47	–	75	2349	26	4.3	2.1	6.4	163	7	9
	1 h., 20 m. p̄		–	–	76	2712	24	4.4	3.2	6.6	179	10	10
20. A. B., P.O. pneumonectomy	ā	N	–	–	62	1870	48	4.5	0.8	5.3	99	–	–
	46 m. p̄		50	–	82	2100	38	5.3	1.8	7.1	149	5	9
	3 h., 35 m. p̄		–	–	87	2090	34	5.1	1.7	6.8	141	4	10

*N, Normal; D, dehydrated.

†S-P, Salt-poor albumin; all other patients received albumin solution containing 0.3 M.NaCl.

1 case of irreversible peripheral circulatory failure due to exposure to cold
1 case of extensive lacerations in a patient with acute alcoholism
2 cases of acute abdominal conditions (incarcerated hernia and thrombosis of mesenteric artery)

Of these 20 patients treated with concentrated human albumin solution only, 17 recovered without the aid of additional intravenous therapy. One patient (Case 2), because of continuous bleeding, received a blood transfusion four hours after the second period of observation. The 2 remaining patients (Cases 6 and 13) who were critically ill on entry to the hospital, died shortly after completion of the third study. It is of interest that although Patient 9 was in mild shock, Patient 17 in moderately severe shock, and Patient 18 in a state of severe dehydration at the time of the first study, all 3 recovered without the aid of additional fluid therapy.

In the majority of instances measurements were repeated within twenty-five minutes of completion of the albumin injection. In four instances, however, this was made between thirty and sixty minutes after completion of the injection. Eleven patients in this group were studied a third time approximately 2½ hours after the injection had been completed.

One-half hour after the end of the albumin injection, the average rise in mean arterial pressure for all 20 cases was 15 mm. Hg. It may be seen in Table I, however, that in two instances there was no rise in blood pressure (Cases 6 and 19) and in one instance there was a fall of 12 mm. Hg (Case 13). If the 2 patients (Cases 6 and 13) who failed to survive are excluded from the calculation, the average rise in mean arterial blood pressure for this group was 17 mm. Hg.

The intravenous injection of concentrated albumin was associated in every case with an increase in plasma volume and a fall in hematocrit. The average increase in total plasma volume for all 20 cases one-half hour after an average albumin injection of 46 Gm. was 520 c.c. Individual increases ranged from 108 to 1,363 c.c. The average increase in plasma volume per gram of albumin injected for the group was 12 c.c. With respect to those individual patients (Cases 2, 9, 10, 17, 19, and 20) in whom there was continuous blood or plasma loss, the plasma volume increase per gram of albumin injected and per gram of albumin retained was expectedly smaller, the average being 7 c.c.

Determinations made upon 11 patients 2½ hours after the injection showed no consistent change in total plasma volume. There was an average further increase of 297 c.c. in 6 cases, an average loss of 257 c.c. in 4 cases, and no change in 1 case. However, figures for the average rise in mean arterial blood pressure and the average increase in plasma volume per gram of albumin injected and retained did not differ significantly from those found at the time of the second period.

Four postoperative thoracoplasty patients receiving the salt-poor albumin solution and 5 comparable patients receiving the standard albumin solution were selected for comparison of the two preparations. Figures for the average

change in each of the measurements made one-half hour after the albumin injection are given in Table II.

It may be seen in Table II that the effects of the salt-poor albumin were, on the whole, similar to those of the salt-containing solution.

TABLE II. COMPARATIVE EFFECTS OF TWO PREPARATIONS OF CONCENTRATED HUMAN ALBUMIN

	INCREASE IN MEAN PRESSURE (MM. HG)	FALL IN HEMATOCRIT (%)	PLASMA VOLUME INCREASE C.C. PER GRAM ALBUMIN	
			INJECTED	RETAINED
Average for 4 patients receiving salt-poor solution	16	5	15	14
Average for 4 patients receiving standard solution	10	7	16	16

The Effect of the Intravenous Injection of Concentrated Human Serum Albumin Upon Plasma Volume, Hematocrit and Serum Proteins When Given With Additional Crystalloid Solution.—The data in Table III have been derived from the study of 18 patients who received at least 400 c.c. of additional crystalloid solution, with 2 exceptions (Cases 2 and 17), in the form of normal saline solution, along with each unit of concentrated albumin, the unit consisting of 25 Gm. of albumin in 100 c.c. of fluid.

The distribution of the 18 cases reported in Table III are as follows:

10 postoperative cases (lung and chest wall resections—abdominal surgery)
4 cases of burn
2 cases of acute abdominal conditions
1 case of multiple lacerations
1 case of gunshot wounds of the abdomen

With the exception of the cases of burn and peritonitis where plasma loss was continuous over a considerable period of time, no additional intravenous therapy was administered. The immediate response to treatment was favorable in all cases.

Measurements were made in this group for the second time approximately one hour after the completion of therapy rather than at twenty-five minutes as in the first group. In twelve instances a third set of measurements was made three hours after therapy had been completed.

The average rise in mean arterial blood pressure in this group at the time of the second period was comparable to that observed in the group receiving concentrated albumin solution alone (17 mm. Hg). However, in 3 patients (2 cases of burn and 1 case of postoperative thoracoplasty) there was little or no change in blood pressure after the administration of the albumin together with about 1,000 c.c. of normal saline solution.

The increase in plasma volume and the fall in hematocrit following treatment in this group of patients was similar to, although larger than, that seen

TABLE III. PLASMA VOLUME AND PLASMA PROTEIN CHANGES FOLLOWING INJECTION OF CONCENTRATED HUMAN ALBUMIN

PATIENT AND DIAGNOSIS	TIME	FLUID STATE*	ALBUMIN INJECTED (GM.)†	FLUID WITH ALBUMIN (C.C.)	MEAN ART. B.P. (MM.)	PLASMA VOL. (C.C.)	HEMATOCRIT %	PLASMA PROTEIN ALBUMIN %	PLASMA PROTEIN GLOBULIN %	PLASMA PROTEIN TOTAL %	PLASMA PROTEIN TOTAL GM.	PLASMA VOLUME CHANGE PER GM. ALBUMIN INJECTED	PLASMA VOLUME CHANGE PER GM. ALBUMIN RETAINED
1. R. S., intest. obstruction	ā	N	–	–	77	2800	42	3.9	2.3	6.2	174	–	–
	13 m. p̄		50	800	100	3430	34	4.4	1.6	6.0	206	13	15
2. M. S., 22 hr. p̄ 20% burn	ā	N	–	–	81	2800	48	4.0	1.5	5.5	154	–	–
	3 h., 45 m. p̄		100	800	94	3375	44	4.5	1.3	5.8	196	6	14
3. M. H., P.O. thoracoplasty	ā	N	–	–	42	2392	28	3.0	2.4	5.4	129	–	–
	50 m. p̄		50	1000	73	3231	22	4.1	1.7	6.0	194	17	14
	3 h. p̄		–	–	66	2867	21	4.0	1.5	5.5	158	10	11
4. B. D., P. O. thoracoplasty	ā	N	–	–	58	1905	33	3.8	2.2	6.0	114	–	–
	43 m. p̄		48	800	91	3710	22	4.2	1.3	5.5	208	38	21
	3 h., 8 m. p̄		–	–	93	3600	21	4.0	1.4	5.4	195	35	23
5. V. W., P.O. thoracoplasty	ā	N	–	–	69	2306	40	4.3	1.6	5.9	136	–	–
	49 m. p̄		50 (S-P)	1000	70	2680	29	4.7	1.0	5.7	153	7	14
	3 h., 10 m. p̄		–	–	75	3070	28	4.6	1.0	5.6	172	15	18
6. M. R., gunshot wound, P.O.	ā	N	–	–	50	2250	50	4.3	1.4	5.7	128	–	–
	1 h., 40 m. p̄		52 (S-P)	1200	78	3230	42	4.4	1.0	5.4	175	19	21
	2 h., 51 m. p̄		–	–	72	2335	44	4.5	1.1	5.6	131	2	10
7. W. S., ext. lacerations	ā	N	–	–	40	1740	38	4.3	1.5	5.8	101	–	–
	1 h., 10 m. p̄		44 (S-P)	700	55	2470	29	4.8	1.2	6.0	148	17	17
8. B. D., P.O. thoracoplasty	ā	N	–	–	64	2600	37	4.2	2.0	6.2	161	–	–
	39 m. p̄		50 (S-P)	1200	70	3150	30	4.6	1.5	6.1	192	11	15
	3 h., 28 m. p̄		–	–	84	3710	29	4.6	1.5	6.1	226	22	18

9. O. W., P.O. thoracoplasty		ā	N	–	–	67	1735	38	4.2	2.0	6.2	108	–	–
	55 m. $\bar{p}$			50	800	81	2570	24	4.6	1.1	5.7	146	17	19
	3 h., 9 m. $\bar{p}$			–	–	86	2350	24	4.7	1.3	6.0	141	12	16
10. M. G., P.O. thoracoplasty		ā	N	–	–	50	2290	32	3.5	2.0	5.5	126	–	–
	41 m. $\bar{p}$			50 (S-P)	800	59	2670	28	4.8	1.6	6.4	171	8	8
	3 h., 45 m. $\bar{p}$			–	–	64	2610	26	4.7	1.5	6.2	162	6	7
11. A. G., P.O. lobectomy		ā	N	–	–	66	2520	41	4.3	2.1	6.4	161	–	–
	20 m. $\bar{p}$			50	800	93	3150	32	4.8	1.3	6.1	192	13	15
	2 h., 36 m. $\bar{p}$			–	–	90	2740	34	5.0	1.5	6.5	178	4	8
12. M. S., P.O., pneumonectomy		ā	N	–	–	67	2580	35	3.3	2.8	6.1	158	–	–
	23 m. $\bar{p}$			50	800	85	4130	27	3.8	1.9	5.7	235	31	21
	2 h., 30 m. $\bar{p}$			–	–	86	3820	29	3.6	2.1	5.7	218	25	24
13. M. M., 21 hr. $\bar{p}$ 30% burn		ā	D	–	–	95	2264	53	3.2	3.3	6.5	146	–	–
	18 m. $\bar{p}$			73	1200	95	2860	40	4.2	2.1	6.3	180	8	13
	2 h. $\bar{p}$			–	–	97	3170	40	3.8	2.3	6.1	194	12	19
14. K. F., 5 hr. $\bar{p}$ 50% burn		ā	D	–	–	89	976	60	2.7	3.4	6.1	60	–	–
	28 m. $\bar{p}$			50	1000	120	1330	46	4.1	1.7	5.8	77	7	13
15. X. D., 3 hr. $\bar{p}$ 25% burn		ā	D	–	–	84	2370	45	4.0	2.9	6.9	164	–	–
	1 h., 32 m. $\bar{p}$			25	900	85	2595	41	4.4	2.3	6.7	174	9	12
16. J. S., P.O. thoracoplasty		ā	N	–	–	53	2875	41	3.4	3.1	7.0	202	–	–
	15 m. $\bar{p}$			49	1000	82	3732	34	4.0	2.3	6.3	235	18	23
	3 h. $\bar{p}$			–	–	88	3482	37	4.2	2.3	6.5	227	12	17
17. S. F., P.O. ruptured viscus		ā	D	–	–	47	2800	51	3.6	0.5	4.1	115	–	–
	1 h. $\bar{p}$			74.5	800	74	3130	41	2.8	2.1	4.9	154	–	–
	2 h., 42 m. $\bar{p}$			–	–	75	3121	43	3.6	1.3	4.9	153	4	27
18. W. H., incarcerated hernia		ā	D	–	–	51	3100	41	3.6	2.2	5.8	180	–	–
	41 m. $\bar{p}$			25 (S-P)	1200	62	3660	34	3.8	2.0	5.8	212	22	21

*N, Normal; D, dehydrated.

†S-P, Salt-poor albumin; all other patients received albumin solution containing 0.3 M.NaCl.

in the previous group. The average increase in total plasma volume for all 18 patients one hour after an average albumin injection of 52 Gm. was 711 c.c. The average increase in plasma volume per gram of albumin injected was 15 c.c. Calculated on the basis of each gram of albumin retained, the increase in plasma volume amounted to 16 c.c. As in the first group, the plasma volume increase per gram of albumin injected and per gram of albumin retained was significantly lower (8 c.c.) in the patients with burn and peritonitis in whom there was continuous loss of plasma.

In the 12 patients in whom a third set of observations was made, changes, although inconstant, indicated a trend toward loss of plasma volume rather than gain when compared to the results obtained in the 11 patients of the preceding group who received albumin alone. Nine cases showed a loss of plasma volume averaging 292 c.c. whereas only 3 showed an increase averaging 520 c.c. Measurements of mean arterial blood pressure and of plasma volume per gram of albumin injected and retained gave approximately the same values at three hours as those obtained within the first sixty minutes after completion of the combined albumin-saline therapy.

The effects of the salt-poor albumin solution given with additional saline to 6 patients in this group did not appear to differ significantly from those seen in the 12 patients receiving the standard preparation together with saline solution.

DISCUSSION

The intravenous administration of concentrated albumin solution given with or without additional fluid in two groups of 20 and 18 patients, respectively, was free from untoward clinical reactions. In most instances, the albumin solution was given rapidly, usually over a period of fifteen minutes or less.

In general, the injection of concentrated human albumin solution alone was associated with an immediate increase in plasma volume of approximately 12 c.c. per gram of albumin injected. Essentially the same average figure was found for each gram of albumin retained. According to the studies of Scatchard, Batcheler, and Brown,[8] this is far below the expected in vitro value of 18 c.c. per gram of albumin. It would appear, then, that in this first group of patients, the albumin retained did not hold a volume of fluid commensurate with its theoretical osmotic activity.

The intravenous administration of 400 c.c. of isotonic saline solution along with the albumin solution resulted in a somewhat greater increase in plasma volume per gram of albumin, both injected and retained, the average being 16 c.c. This figure compares more favorably with the theoretical value of 18 c.c. With respect to the osmotic activity of concentrated albumin in vivo, the volume of fluid held by each gram of albumin in the experience of others covered a considerable range. In the series of Cournand and associates,[2] each gram of albumin retained held 23 c.c.; in that of Heyl and co-workers,[1] the average figure for each gram of albumin injected was 17.4 c.c.; whereas in the series of Warren and associates,[3] the figure was 16 c.c. per gram of albumin injected. In a more recent study by Stead and co-workers[4] the figure was 14 c.c. This range of values is, perhaps, to be expected on the basis of (1) differences in the degree of hydra-

tion of patients, (2) differences in the amount of fluid given intravenously along with the albumin, and (3) differences in the type of clinical condition (medical, traumatic, etc.) studied.

Patients in severe shock, presumably with continuing blood or plasma loss, showed much smaller increases in plasma volume per gram of albumin given and retained (8 c.c. average in shock against 14 c.c. average in nonshock cases). In a case of severe shock, therefore, the administration of 100 c.c. of concentrated albumin (25 per cent) without additional fluid corresponds to no more than 200 c.c. of plasma.

Although, in the majority of instances, the increase in total circulating protein after the injection of albumin was approximately equal to the amount given, it should be noted that in 25 per cent of the cases studied, this increase was significantly greater than expected. This observation suggests the possibility that during recovery protein may be mobilized from body reserves or that blood, in static pools during the hypotensive period, may be returned to the circulating blood stream as the state of the general circulation improves. Errors in laboratory determinations are, of course, a possibility, but the gain in protein over and above the amount injected far exceeds that considered due to the error of the method, that is, ±0.2 per cent.

In spite of the fact that a rise in intra-arterial blood pressure followed the intravenous injection of concentrated albumin in group I and of concentrated albumin with additional fluid in group II, the blood pressure failed to reach accepted normal levels. This observation has been noted previously by Cournand and associates,[2] who studied the effects of concentrated human albumin therapy upon the dynamics of the circulation. Their results showed clearly that changes in mean arterial blood pressure are not a reliable index of changes in cardiac output and that although cardiac output and intra-auricular pressure (venous return) attain normal levels after the intravenous injection of concentrated albumin solution, the blood pressure may remain subnormal. It was also pointed out that with hemodilution there would be a decrease in blood viscosity. This may account, at least in part, for the failure of the blood pressure to rise to accepted normal levels. Further evidence that changes in viscosity play an important role in the variation of peripheral resistance was obtained in a study on the intravenous use of a gelatin solution of high viscosity in the treatment of shock.[9] In this latter study, the increase in blood pressure was relatively greater than the increase in cardiac output.

Of 3 patients in the first group (Cases 6, 13, and 19) who showed no increase in mean arterial blood pressure after the injection of albumin, it is of interest to note that the one patient who survived (Case 19) was the only one of the three who did not show a significant increase in plasma volume. In contrast, the 2 patients who seemed from the start beyond the resources of replacement therapy and who later died showed a rapid increase in plasma volume. It is suggested that this latter sequence of events may be of some prognostic value. A rapid increase in plasma volume in the presence of a stationary or falling blood pressure after the intravenous injection of albumin may indicate failure in vasomotor tone.

A further point of interest lies in the fact that these 2 patients (Cases 6 and 13) retained as much albumin in the circulation as did the surviving group of patients. This observation speaks against the concept that a generalized increase in capillary permeability is characteristic of irreversible shock.

CONCLUSIONS

1. In a group of 20 patients requiring fluid replacement, the intravenous injection of concentrated human albumin solution given without additional intravenous fluid was associated with a fall in hematocrit and a rapid increase in plasma volume amounting to 12 c.c. per gram of albumin given. Approximately the same average figure was found per gram of albumin retained. The average increase in plasma volume in the 6 patients who were in shock was smaller than the average for the entire series (7 c.c. per gram of albumin injected and retained).

2. The administration of 400 c.c. of isotonic saline solution along with the albumin solution to a group of 18 patients resulted in a greater increase in plasma volume as compared to the increase when albumin solution was given alone: 15 c.c. per gram of albumin injected; 16 c.c. per gram of albumin retained. In the cases of burn and peritonitis where there was continuous plasma loss, increases in plasma volume after the combined albumin-saline therapy were expectedly smaller (8 c.c. per gram of albumin injected and retained).

3. The average injection of 46 Gm. of concentrated human albumin solution alone produced an average rise in mean arterial blood pressure of 17 mm. Hg. The same average rise was observed after the administration of albumin together with additional intravenous saline solution.

4. The effects of the salt-poor albumin solution given with and without additional saline solution did not differ significantly from those of the standard salt-containing albumin solution given with and without additional saline solution.

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ACUTE PHLEGMONOUS GASTRITIS

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ACUTE phlegmonous gastritis is a nonspecific infection of the stomach wall characterized by seropurulent or fibrinopurulent inflammation usually involving all the gastric layers to some extent, but affecting chiefly the submucosa.

Although first described by Galen, the condition has been reported relatively infrequently in the literature. The first case described in modern medical writing was reported by Cruveilhier in 1820. By 1905, 50 cases were collected; in 1919 Sundberg[1] reviewed a series of 215 cases including 17 cases of his own. In 1937 Fink[2] was able to bring the total to 306. Approximately 29 new cases have been described during the past nine years, for a total of 335 cases to date.

The etiology of acute phlegmonous gastritis is not entirely clear, although a number of theories have been advanced.[3] The organism involved, when cultures have been taken, is hemolytic streptococcus in over 70 per cent of the cases.[4] Many other organisms have been encountered however, including staphylococcus, pneumonococcus, *Bacillus coli, Bacillus subtilis, Bacillus proteus,* and *Bacillus welchii.*[5]

The pathologic process may be initiated in one of two ways; either as a local condition, or metastatic from a distant focus of infection. In the former, some pre-existing pathologic condition such as carcinoma, atrophic gastritis, ulceration associated with corrosive poisoning, or a surgical procedure on the stomach, allows the initiation of the inflammatory process. It is somewhat difficult to visualize how the infecting organisms are able to remain active in the presence of gastric secretion, but as Sundberg pointed out, many of the patients falling into this locally initiated group have a hypoacidity for one reason or another. In line with this, Symmers was able to show that dogs suffered no ill effects when fed a mixture of streptococci and ground glass.[6] However, Doehle has produced phlegmonous gastritis by feeding streptococci to dogs whose stomach mucosa had previously been damaged by alcohol ingestion.

In the larger group of patients, no definite break in the mucosa is found and it is believed that the infection is metastatic, possibly on an embolic basis, from a distant focus of infection. Cases have been reported following tonsillitis (Brooks and Clinton),[7, 8] stomatitis, furunculosis (Gerster),[9] otitis media (Barnett and Harris),[10] erysipelas, drainage of an oral infection, or extraction of an infected tooth. Mortland and Eisenberg[11] noted that several cases were found at autopsy associated with a puerperal sepsis epidemic in Prague in 1847, though the condition is rare as an accompaniment of a septicemia.

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In 80 per cent of the cases, the patients fall into an age group of from 30 to 60 years and the condition is three times as common in men as in women.[12] When the disease occurs in younger individuals it is usually associated with an acute infectious process such as measles, scarlet fever, or streptococcic pharyngitis as in the case reported by Cutler and Harrison.[13]

Early observers of phlegmonous gastritis described the post-mortem findings as a "carbuncle of the stomach" (Virchow) or as erysipelas of the stomach, the cutaneous analogy being striking after examination of the pathologic material. Two varieties of the disease are described, the localized and the acute diffuse types. In the former, a classical example of which was reported by Novak,[14] the process is well demarcated and consists of a walled off abscess cavity involving chiefly the submucosa with some destruction of the muscularis; the original inflammatory reaction usually has resulted in numerous adhesions to surrounding structures. The early symptoms of this type are somewhat similar to those of the acute form and the chronic phase may be the end result of an acute attack.[15] With the establishment of the abscess cavity, the symptoms are chiefly those of obstruction caused by the tumor mass.

In the acute diffuse form, the entire stomach or merely a portion of it may be involved.[16] It is usually stated that the process shows sharp limitation to the stomach alone, although Greaves reported two cases discovered at autopsy where a part of the duodenum was also involved.[17] The process may vary from early inflammation in some areas to complete gangrene with perforation in others. The mucosa is usually intact and shows evidence of lymphocytic infiltration and edema. There may be thromboses present and also areas where extravasation of blood has taken place. As in the localized form, however, the major pathologic changes are found in the submucosa which may form two-thirds of the thickness of the gastric wall. In this layer the typical severe inflammatory reaction accompanied by massive polymorphonuclear infiltration is encountered. The muscularis and serosal layers show varying degrees of involvement from edema to necrosis depending on the extent of the primary process in the submucosa. Untreated, the process resolves by perforation either into the gastrointestinal tract, which may result in a spontaneous cure, or into the abdominal cavity causing a peritonitis, which is fatal in over 90 per cent of the cases. Death may occur without peritonitis, however, and it is believed to be the result of the toxemia accompanying the disease.[18] Early recognition or suspicion of the condition, however, followed by prompt and adequate therapy may alter this grave prognosis in the future.

The signs and symptoms of the disease in its acute form are those of an acute lesion in the upper abdomen, plus sepsis.[19] Severe epigastric pain is generally the earliest symptom; it is rather sudden in onset, continuous, and quite well localized before perforation. Vomiting is usually, but not necessarily, present and contrary to what might be expected the vomitus rarely contains pus. The temperature and pulse rate are usually high, and a leucocytosis of 20,000 to 30,000 with a marked shift to the left is common. The pain is localized, not referred to the back, and usually becomes continuously worse. Tender-

ness is localized to the epigastric area until a spreading peritonitis develops. It was noted by Deininger in 1879 that the pain in phlegmonous gastritis is relieved when the patient sits up (Deininger's sign). Fluoroscopic examination of the upper gastrointestinal tract reveals an atonic stomach with loss of the mucosal pattern, and barium retention may be complete.

Among the various conditions which must be considered in the differential diagnosis of acute phlegmonous gastritis are perforated ulcer (either gastric or duodenal), acute pancreatitis, acute cholecystitis, cholelithiasis, and basal pneumonia. However, only one author has reported making this diagnosis correctly, and it usually becomes apparent only at operation or necropsy.[20]

The treatment as reported in the literature has not yielded very encouraging results.[2, 21] Gastric resection has been performed on some patients, but the mortality is practically 100 per cent unless one is dealing with the localized form of the disease which may respond to this treatment. Cutler and others have used a simple gastrostomy with success. Eliason and Murray-Wright have suggested a gastrotomy with incision of the mucosa for drainage into the gastrointestinal tract. In the very rare cases in which the patients recover without operation, this process may occur spontaneously and thus allow satisfactory drainage without peritonitis, or a walled off abscess may form which could result in the chronic type of the disease.[15]

In the case we are reporting, the operative procedure was similar to that used by Eliason and Murray-Wright, which employs the sound surgical principle of drainage of an abscess cavity. If no localization is found, it is doubtful that any operative procedure on the stomach is justified. Since the infecting organism in this case was the hemolytic streptococcus, as it is in the majority of them, penicillin was used in large doses and we feel this was significantly responsible for the patients relatively benign postoperative course.

CASE REPORT

The patient was an 18-year-old white male who had been admitted to the hospital on May 19, 1946, with a diagnosis of measles. He had previously been in good health with no history of gastrointestinal disturbances. On the afternoon of May 31, 1946, after what had been an uneventful convalescence, the patient complained of the sudden onset of a rather severe nonradiating epigastric pain accompanied by nausea but no vomiting. Examination revealed acute well-localized epigastric tenderness with some spasm but no rigidity. Temperature was 100° F., pulse 90, respirations were 28. White blood cells were 24,000 with 72 per cent polymorphonuclear cells. X-ray view of the chest was negative and a roentgenogram of the abdomen revealed no gas beneath the diaphragm. Bowel sounds were present. He was placed on penicillin and watched through the night.

The following morning the patient's temperature had dropped to 99.2° F.; pulse and respirations remained the same. There was no change in the physical examination at this time. Serum amylase level was 114 units. During the course of the day, however, the epigastric pain began to increase in severity and to become somewhat less localized. Rebound tenderness referred to the epigastrium was noted. There was still no vomiting. By afternoon the temperature had risen to 101.4° F.; pulse 120; respiration 32. The chest was clear to auscultation. Only an occasional bowel sound was present in the lower abdomen. White blood cells remained at 24,000; urine examinations were negative. Surgical intervention was decided upon and a preoperative diagnosis of perforated gastric ulcer was made.

The abdomen was opened through a high right transrectus incision, and a slightly turbid fluid was encountered free in the peritoneal cavity. The stomach was found to be markedly indurated in the distal two-thirds, but the process stopped abruptly at the pylorus. Low in the antral indurated portion there was a fluctuant mass measuring about 3 cm. in diameter over which the omentum had become adherent. On aspiration this yielded frank pus and blood.

After carefully walling this area off with lap pads, the abscess was opened. The mucosa underlying it was found to be intact, and an opening was made into it allowing drainage into the stomach cavity. The incision into the abscess was then closed with four heavy sutures through the serosa and muscularis and the omentum was tacked down over the area. Five grams of sulfanilamide powder were placed in the peritoneal cavity. The wound was closed without drainage. Culture of the material aspirated from the abscess yielded hemolytic streptococcus.

The patient was placed on continuous Wangensteen suction postoperatively; he received daily 1000 c.c. 5 per cent dextrose in distilled water, 1000 c.c. five per cent dextrose in normal saline solution, and either 1000 c.c. of amigen or 500 c.c. of whole blood according to his requirements, which were followed by frequent blood counts and blood chemistries. He was also given penicillin (50,000 units every three hours) and intravenous sodium sulfadiazine, 2.5 Gm. twice daily. He passed some gas per rectum on the second postoperative day although the stomach did not empty well until the seventh postoperative day when the Levine tube was removed. Temperature had returned to practically normal on the third and fourth postoperative days, but on the fifth postoperative day it started to rise again. White blood cells were 7,800 and urine was negative. The wound was healing well without evidence of infection and examination of the abdomen showed minimal tenderness. The chest was clear and there was no evidence of phlebitis. Although the blood level of sulfadiazine was only 4.4 mg. per cent it was felt that the fever was due to reaction to the medication. Sulfadiazine was stopped on the eighth day and while the temperature rose to 103° F. that day, it rapidly returned to normal on the following day and remained essentially so for the rest of the hospitalization period.

Two weeks postoperatively he was up and around and on a high protein diet. Penicillin was stopped on the eighteenth postoperative day. The patient had lost about twenty pounds during the course of the illness. In spite of eating rather well, however, he failed to gain weight and the plasma protein remained around 5.5 Gm. per 100 c.c. He was unable to tolerate a high protein, high caloric formula or oral amigen, so amigen or plasma were given intravenously for ten days. At the end of this time he had gained five pounds, the proteins rose to 6.40 Gm. per 100 c.c., and he felt much stronger. Four weeks postoperatively he was sent home on a twenty-day leave.

On return to the hospital, the patient looked well although he had not gained any more weight. Fluorscopic examination of the stomach at this time revealed a perfectly normal stomach mucosa; there was no demonstrable evidence that an operative procedure had been performed. The patient was discharged to duty three months after operation.

SUMMARY

A discussion of the problem of acute phlegmonous gastritis has been presented. The mortality in previously reported series varies from 84 to 92 per cent.

A case was reported in which the patient was treated with gastrotomy for drainage of a fluctuant area which was part of a diffuse inflammatory process. Adequate doses of penicillin were given postoperatively in combination with intravenous sulfadiazine. The patient recovered.

It is believed that, where the organism involved responds well to antibiotic agents, adequate surgical drainage of localized abscesses in conjunction with use of the indicated drug may well bring about a significant reduction in the present mortality figures for this disease.

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THE RADIOGRAPHIC DIAGNOSIS OF PERFORATIONS OF THE UPPER GASTROINTESTINAL TRACT INTO THE MEDIASTINUM AND PLEURAL CAVITY

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DESPITE the advances made in recent years in the diagnosis and treatment of lesions of the esophagus, one lesion still presents an extremely high mortality rate, namely, esophageal perforation. As Wagner stated in his very fine paper on the subject, "The tragic fate (esophageal perforation) can almost never be averted by surgical intervention, even if the surgery is carried out by the most skillful surgeon."

Fortunately this is not always the case, as the prognosis depends in part on the location of the perforation in the esophagus. Perforations high in the esophagus have a better prognosis than those lower down. Mörl gave several reasons for this. First, in perforations of the cervical portion of the esophagus, the tendency is for the resultant inflammatory process in the mediastinum to spread upward where it is more easily accessible to surgical intervention. Second, the inflammatory process in the superior mediastinum appears to lead to a more limited process than that resulting from a perforation lower in the esophagus. Finally, the relatively easy accessibility to the site of perforation, not only from the outside, but also from within, with the aid of the esophagoscope, makes it less dangerous. The duration of the underlying pathology before the time of perforation also appears to alter the extent of the resultant mediastinitis. In perforations of the esophagus secondary to a long-standing process, there is a tendency toward a localized periesophagitis rather than a diffuse mediastinitis. This is apparently due to walling off of the inflammatory process from the fibrosis attending the underlying chronic esophageal lesion. Perforations of the lower esophagus commonly rupture into the pleural cavity, with an invariably fatal outcome. Mörl believed that recovery in these cases belongs to the "great rarities of clinical medicine."

Immediately above the diaphragm, the esophagus and mediastinal pleura are in close apposition. Also, this portion of the esophagus has been shown experimentally by Weiss and Mallory (quoted by Eliason and Welty), Mackenzie and Taylor, and Thalheim, Brosch, and Bencke (quoted by Wagner) to be the weakest, and it is here where, under increased pressure from vomiting or coughing, spontaneous perforation occurs and the pleura is most often torn. Numerous authors (Williams and Boyd; Brown; Collis, Humphreys, and Bond; Mörl; Eliason and Welty) have reported such cases of esophageal rupture where at autopsy no apparent cause for the perforation could be found. Perforations higher in the esophagus may result from a number of causes;

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among these are foreign bodies, instrumentation, and perforation of a pre-existing lesion, such as diverticulum, ulcer, or carcinoma.

Smead (quoted by Wagner) reported a case of esophageal perforation below a stricture in a 50-year-old man who was known to have a chronic duodenal ulcer. A preoperative diagnosis of perforated duodenal ulcer was made; however, at operation a volvulus of the lower bowel was discovered. The patient died thirty-six hours following the operation. Autopsy findings were pyloric stenosis, collapse of the left lung, pleural empyema, an esophageal stricture 5 cm. above the diaphragm, and, between this and the diaphragm, a 2 cm. long perforation into the mediastinum and left pleural cavity.

Smead explained the perforation on the basis of vomiting as a result of the volvulus. Because of the pyloric stenosis and esophageal stricture, the stomach could not empty quickly enough during the act of vomiting and a perforation resulted.

We have had the opportunity of observing four cases of perforation of the esophagus into the mediastinum and/or pleural cavity. In two of the patients the etiology was peptic ulcer of the lower esophagus and cardioesophageal junction.

In the others, the perforations were secondary to instrumentation. Three of the patients died within a short period of time following the initial symptoms. The fourth patient apparently experienced a perforation high in the esophagus with a resultant emphysema of the neck, and mediastinitis. The pleura was not involved and she made an uneventful recovery.

The two patients showing ulcers had been consuming alcoholic beverages at or shortly prior to the onset of symptoms. In each a considerable quantity of alcoholic smelling pleural fluid was withdrawn before death in an effort to alleviate the discomfort in the chest. It is interesting that in three cases reported by Eliason and Welty, the perforations in two were preceded by bouts of vomiting and retching. One of these was a known alcoholic who had recently been on a prolonged drinking spree. Perforation in the third patient followed an operation for a low small bowel obstruction. While vomiting had preceded the perforation in this case it was not considered by the authors to be a prominent feature in the history. In cases of esophageal perforation observed by Raestrup, Vinson, Girard, and Kissel (quoted by Wagner), the seat of the perforation arose by sudden overstraining of the esophagus caused by either severe choking or vomiting.

It would appear from reviewing the literature and also from the following histories in two of our cases, that a sudden increase in pressure, such as that resulting from a blow to the abdomen or from vomiting and retching, is a contributing factor in the etiology of spontaneous esophageal perforation.

CASE REPORTS

CASE 1.—The patient, a 51-year-old white man, was admitted to the Buffalo General Hospital late in the evening with the history of headache, nausea, and precordial pain since afternoon. Just before supper he took several drinks of whiskey thinking it would "settle his stomach" before eating. Suddenly he became extremely nauseated. This was followed by vomiting and sharp precordial pain which radiated to the lower left side of the chest, abdomen, and left groin.

A roentgenogram of the chest and abdomen showed a left hydropneumothorax with practically complete collapse of the lung. The heart and mediastinum were markedly shifted to the right. No free air was demonstrated in the peritoneal cavity. The patient died approximately twelve hours after admission.

The autopsy in part revealed a 1.2 by 0.4 cm. acute perforation in the lower esophagus, just above the level of the diaphragm, the perforation opening into the posterior mediastinum and into the left pleural cavity. The left pleural cavity contained about 2 L. of regurgitated gastric content, with particles of vegetable matter being very apparent. The entire mediastinum was markedly shifted to the right and the entire left lung was completely collapsed. There was marked inflammatory edema of the posterior mediastinum with a fair amount of purulent exudate surrounding the esophagus.

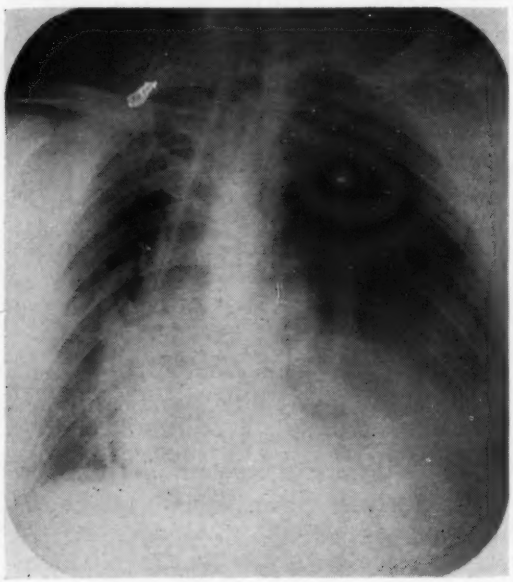


Fig. 1.

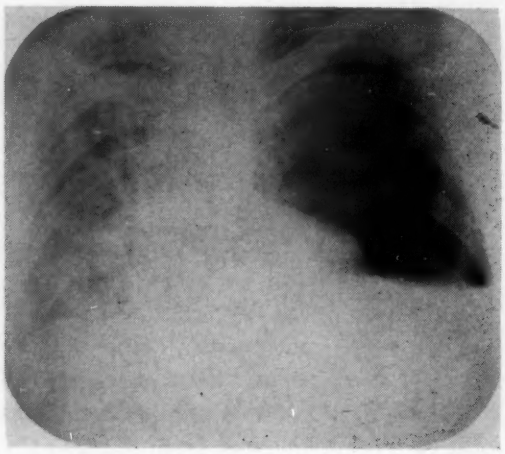


Fig. 2.

Fig. 1 (Case 1).—Semiupright view of the chest; tension hydropneumothorax is readily recognized.

Fig. 2 (Case 2).—Upright view of the chest; tension hydropneumothorax is as noted in Case 1. On the original roentgenogram subcutaneous emphysema in the upper chest could be recognized more readily than on this reduction.

CASE 2.—The patient was a white man, aged 35 years, admitted to the Buffalo General Hospital in the morning with a history of occasional epigastric distress (known duodenal ulcer). The previous night he had experienced nausea followed by emesis. Shortly afterward he had sudden, sharp pain in the lower part of the chest and pain radiating across the scapulae. On arrival at the hospital the patient was in shock, and appeared cyanotic and orthopneic.

A roentgenogram of the chest taken on admission revealed practically complete collapse of the left lung by a hydropneumothorax, fluid level reaching the eighth interspace posteriorly. The heart and mediastinum were shifted to the right. There was also marked subcutaneous emphysema of the neck and upper chest. The patient died that same evening.

The autopsy revealed in part a somewhat triangular shaped peptic ulcer situated in the anterior and left lateral portion of the cardioesophageal junction with broad and massive perforation of the upper two-thirds of the lesion into the mediastinum. The entire ulcer measured 2.8 by 0.7 cm. A second typical chronic ulcer, oval shaped and measuring 1.2 by 0.6 by 0.4 cm., was situated in the superior aspect of the first portion of the duodenum. There was a very marked mediastinitis involving the posterior mediastinal structures, particularly inferior to the level of the clavicles, with a great deal of dark greenish-

A. *B.* *C.*

Fig. 3 (Case 3).—*A*, Roentgenogram made on admission, showing tension hydropneumothorax. *B*, Roentgenogram on Case 3 made the day following admission with suction needle in place. The return of the mediastinum to normal position can be noted. *C*, Roentgenogram after suction was removed from left side of chest. Again the hydropneumothorax is under tension and the mediastinum is deviated.

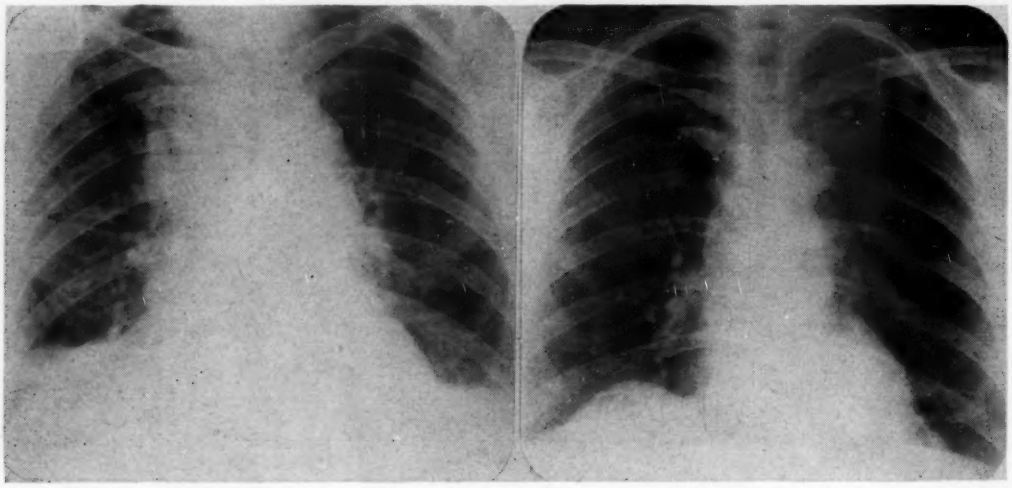
brown stomach content and fibrinous exudate in the mediastinal soft structures particularly surrounding the perforated lesion. The mediastinal parietal pleura of the left chest overlying the site of perforation showed very distinct peptic digestion in an area measuring 3.5 by about 2.5 cm. with broad communication between the mediastinum and the left pleural cavity. There was a marked left pneumohydrothorax with between 1,500 and 2,000 c.c. of fluid and stomach content in the left pleural cavity, including several particles of partially digested food.

CASE 3.—The patient, a 47-year-old woman, was admitted to the Buffalo General Hospital a few hours after esophageal dilatation with complaints of pain in the left lower part of the chest and epigastric distress. She had complained of dysphagia for approximately one year and esophagoscopy had revealed a mild cardiospasm.

A chest roentgenogram at the bedside revealed marked displacement of the mediastinal structures toward the right, and a left hydropneumothorax.

The patient had a septic course, and fluid aspirated from the left side of the chest shortly after admission resembled ingested liquids. Repeated chest taps subsequently revealed thick, foul, pale yellow exudate. The patient continued a steadily downhill course and died nineteen days after admission.

Serial roentgenograms of the chest showed no appreciable change in the appearance of the left hydropneumothorax. Permission for autopsy was not obtained.



A. *B.*

Fig. 4 (Case 4).—*A*, Posteroanterior view made at time of admission showing diffuse mediastinal widening and subcutaneous emphysema in the upper chest; *B*, recheck view following recovery, demonstrating return to normal.

CASE 4.—The patient was a 61-year-old woman who was admitted to the Brook's Memorial Hospital, May 12, 1946, with the complaints of chest pain, difficulty in breathing and swallowing, and pain in the abdomen. Temperature on admission was 102.8° F., rectal, pulse 130, and respiration 38.

The patient had been esophagoscoped the previous day for unexplained difficulty in swallowing. She was extremely uncooperative during the procedure, which was carried out with difficulty under local anesthesia.

Physical examination at time of admission revealed rather marked subcutaneous emphysema involving the neck. A roentgenogram of the chest showed diffuse widening of the mediastinum, apparently resulting from a diffuse mediastinitis. The pulmonary fields revealed a linear area of fibrosis just above the left diaphragm, otherwise nothing unusual.

The patient was treated symptomatically and the emphysema and pain lessened. The temperature gradually came down so that by the tenth day it was normal. She was discharged on May 22, 1946, greatly improved.

Three of the four cases presented illustrate rather massive esophageal perforations into the pleural cavity with resultant hydropneumothorax. The fourth case illustrates a perforation high in the esophagus in which the pleura was not involved. The patient experienced a moderately severe mediastinitis from which she recovered.

We feel that the radiographic finding of hydropneumothorax in a patient who experiences sudden onset of chest and/or abdominal pain, accompanied by shock and collapse, is diagnostic of a perforation of the upper gastrointestinal tract, either lower esophagus or stomach, into the mediastinum and pleural cavity. Spontaneous pneumothorax should be readily differentiated radiographically from pneumothorax occurring secondary to esophageal perforation by the absence of an associated pleural effusion. The lung following a spontaneous collapse usually re-expands without a complicating effusion, however, if fluid forms, it is not until some time after the initial collapse. In cases of esophageal perforation, on the other hand, the collapse and formation of fluid occur simultaneously.

In reviewing the literature on this subject, it was found that when a plain x-ray view of the chest was taken showing a hydropneumothorax, it was rarely regarded, per se, as being a *diagnostic criterion* of esophageal perforation, but was thought of primarily as confirming the clinical finding of a pulmonary collapse. Many of the cases reported (described later in this paper) showed radiographic evidence of sudden onset of hydropneumothorax, however, the diagnosis of esophageal perforation was not made until sometime later, or until after death. In other instances, the chest roentgenogram was used as an adjunct for determining the amount of soft tissue swelling and emphysema, thereby following the progress of the condition. Eliason and Welty concluded from their study of the subject, that spontaneous rupture of the esophagus is much more common than appreciated, and that in most instances the diagnosis is not made until the patient comes to autopsy. This is probably due in part to the varied symptomatology which esophageal perforation presents, suggesting coronary occlusion, pulmonary embolism, dissecting aortic aneurysm, spontaneous pneumothorax, acute pancreatitis, gastric perforation, or mesenteric thrombosis, and, furthermore, to the fact that it is not thought of in the differential diagnosis when the patient is first seen. One of their cases was definitely diagnosed radiographically before death by the presence of air in the mediastinum.

Friedenwald and Morrison reported three cases of perforation through esophageal carcinomas secondary to instrumentation. One of their patients showed a hydropneumothorax radiographically. They stated that the rapid development of a hydropneumothorax is a "suggestive sign" of esophageal perforation. Smead emphasized the mediastinal widening and emphysema as being indicative of a perforation of the esophagus. Collis, Humphreys, and Bond likewise believed that the most valuable diagnostic signs of esophageal

perforation are the deep emphysema in the neck and physical findings indicating fluid or air in the chest. These signs, according to these authors, together with the radiographic evidence of a mediastinitis in a patient who experiences a sudden onset suggesting a perforated peptic ulcer, coronary occlusion, or spontaneous pneumothorax, should confirm the diagnosis.

Ballin and Saltzstein reported a case of perforation into the pleural cavity which was thought at first to be a gastric perforation because of the abdominal and diaphragmatic rigidity, and the respiratory distress. An abdominal laparotomy, however, was negative. The patient subsequently died, and a large left hydrothorax and a perforation of the esophagus into the left pleural cavity secondary to an ulcer two inches above the diaphragm were found at autopsy. No roentgenograms of the chest were taken. Benson and Penberthy reported a case of esophageal perforation secondary to an ulcer in a child of 2 years of age with recovery. The patient had been esophagoscoped four hours previously. A plain, x-ray view of the chest showed a tension pneumothorax with pleural effusion. These authors concluded that, together with the knowledge that the ulcer existed, the finding of the hydropneumothorax strongly suggested esophageal perforation.

In the case reported by Wallfield, the perforation was not suspected despite the radiographic finding of a hydropneumothorax, until after yeast and *Bacillus acidophilus* were recovered from the pleural fluid. Subsequent fluoroscopic examination during the ingestion of iodized poppy-seed oil showed a communication of the lower esophagus with the right pleural cavity. The patient presented a vague history of having swallowed a chicken bone three weeks prior to death (the day of onset of symptoms). Gott concluded from four cases he observed that a sudden onset of pain in the lower part of the chest coming on during vomiting and associated with hematemesis, subcutaneous emphysema of the neck, respiratory distress, and prostration are pathognomonic of esophageal rupture. One of his patients was x-rayed and showed a hydropneumothorax. All four showed hydropneumothorax at autopsy.

Baumevieille in his excellent article on pleural manifestations in esophageal perforations stressed pleuropulmonary manifestations as being an important diagnostic sign of esophageal perforation in patients who present a history of swallowing a foreign body or caustic fluid. In the majority of cases studied by this author, the pleura became involved, and it is the pleural complications in particular that suggest perforation of the esophagus. In Roszak's case, the diagnosis was not made until after gastric contents were removed from the left pleural cavity. A subsequent chest roentgenogram confirmed the presence of a left hydropneumothorax.

Aldrick and Anspach reported an interesting case of esophageal perforation in a 6-month-old child as a result of a blow to the upper abdomen from a fall. X-ray view of the chest taken eight hours after the accident showed a right pneumothorax. The second view of the chest taken the second day revealed a massive right pleural effusion. Despite this radiographic evidence, its full significance was not realized, and the perforation was not suspected

until gastric contents were subsequently removed from the right pleural cavity. The patient died within forty-eight hours from the time of the accident.

Several of the authors cited have given contrast media by mouth in order to visualize the communication between the esophagus and pleural cavity. Smead agreed that it is an impractical and hazardous procedure. Mörl stated that the demonstration of the perforation by oral barium is undesirable in the active stage because of the condition of the patient. He believed it to be indicated, however, if the patients have withstood the perforation for several days. He qualified this statement by saying, "if care is taken to give only small portions of barium, then the patient can certainly not be harmed, but the experiment may clear up many a pathologic relationship and give indications for further therapy." In two of Wagner's patients, contrast media was given and in each it was seen under the fluoroscope to pass into the main stem bronchus. Berger (quoted by Wagner) reported a case of death by asphyxia shortly after the administration of barium by mouth.

In the patients who withstand the perforation, the upper or cervical portion of the esophagus is usually the seat of the perforation, and the pleural cavity is not secondarily involved. It is in these patients that barium may be given by mouth to substantiate the diagnosis. Where there is marked pleural involvement, indicative of a perforation lower in the esophagus with a free communication between the esophagus and pleural cavity, it is undesirable for obvious reasons to give contrast media by mouth. We believe that the scout chest x-ray view offers one of the best criteria for a diagnosis in these cases, and that the administration of contrast media would be of academic interest only.

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VOLVULUS OF THE SIGMOID COLON AND ITS TREATMENT

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DEFINITION

CLINICALLY speaking the term volvulus means a torsion of the bowel on its mesentery which cause symptoms, whether the symptoms are caused by narrowing of the bowel, strangulation of the blood vessels, or both (Laurell). This definition includes not only volvulus with an acute course but subacute and chronic cases as well.

OCCURRENCE

According to statistical studies, volvulus of the intestinal tract accounts for 30 to 50 per cent of the intestinal obstructions in the eastern European countries (Finland, Russia, the Baltic States, and others). In western European countries and the United States volvulus makes up about 10 per cent of the total intestinal obstructions.

The presence of a movable mesentery to give the bowel mobility is a prerequisite for volvulus. Therefore, volvulus is localized in the stomach, small bowel, cecum, transverse or sigmoid colon, but not in the retroperitoneal parts of the bowel.

LOCALIZATION

In large statistics, volvulus of the small bowel usually makes up 25 to 35 per cent of the entire number of volvulus cases. In his study of 320 cases, the Finnish surgeon Lennart Peterson found that volvulus of the small bowel made up 24 per cent.

Volvulus of the large bowel is the most common. In most cases the site of the lesion is in the sigmoid colon.

The Ullevaal study of volvulus of the sigmoid which includes cases from Department II and Department III shows a marked increase in the number of patients treated during the war years, that is, 85 of the patients were treated after September, 1939.

AGE AND SEX DISTRIBUTION

Volvulus of the sigmoid is seen rarely in individuals under 30 years of age. Among the ninety-one cases mentioned in Table I under the Ullevaal heading, there were only four patients under 40 years of age, while fifty-seven were over 60 years. Volvulus occurs more often in men than in women because the female pelvis is wider and the abdominal wall, particularly after pregnancies, is more relaxed. Therefore, the loops of the bowel have more room to

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TABLE I. DIVISION INTO DIFFERENT TYPES OF VOLVULUS

TYPE OF VOLVULUS	PETERSON, FINLAND	EDGREN, FINLAND	LAURELL, SWEDEN	TUOVINEN, FINLAND	ULLEVAAL, DEPT. II & III
Cecum	108	7	1	17	7
Transverse colon	6		3	1	4
Sigmoid colon	128	14	26	25	91

move about and a beginning volvulus in women has a greater possibility of spontaneous reduction. Of the patients in Peterson's study, 86 per cent were men; at Ullevaal 61 per cent were men.

ETIOLOGY

Conditions Predisposing to Volvulus of the Sigmoid

1. A long and freely movable sigmoid colon. An increase in length of the sigmoid colon may be caused by chronic constipation, volvulus attacks of a passing nature, spontaneously repaired, or kink torsion. A diet high in vegetables and residue such as is common in eastern European countries and in countries on war rations is a contributing cause of volvulus of the sigmoid.

2. A long and freely movable mesosigmoid.

3. A sigmoid loop whose limbs lie close together. This condition is present in a mesosigmoid with a small fixation angle to the posterior abdominal wall, and is also caused by shrinking mesosigmoiditis which is probably the result of previous attacks of volvulus, constipation, or possibly diverticulitis. In the Ullevaal study, sixteen of the eighteen patients operated upon or examined post mortem had shrinking mesosigmoiditis.

The location of the sigmoid colon varies with the amount and weight of contents and the position of the body. The most moderate form of volvulus of the sigmoid is a clockwise torsion of 180 degrees, described by Wilms as physiologic volvulus. This is not usually accompanied by intestinal symptoms, and x-ray examination shows that it usually repairs itself spontaneously without any sign of obstruction of the bowel or disturbance of circulation. In 180 degree counterclockwise torsion of the sigmoid, the proximal sigmoid loop may be squeezed between the distal scybala-filled sigmoid loop and the posterior abdominal wall causing obstruction and a circulatory disturbance in the sigmoid flexure.

PATHOGENESIS

Wilms believed that volvulus which causes symptoms develops from the symptom-free 180 degree physiologic volvulus in most cases. The rectal loop which lies behind the colonic loop may be gradually filled with gas and stool because of retention. The heavy rectal loop then changes its position and falls in front of the emptier colonic loop, possibly as a result of a movement of the body to the right. Thus, torsion of 360 degrees is accomplished.

The intensity of the occlusion and strangulation increases with the increased degree of torsion, but it is chiefly as a result of tension and limitation of the torsion site that complete occlusion and strangulation occur. Volvulus of more

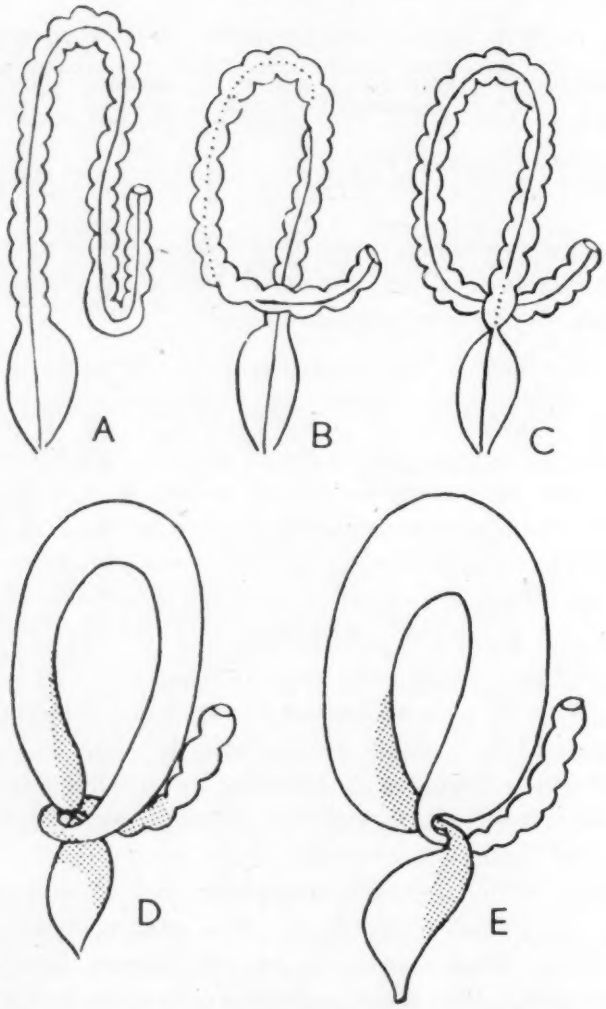

Fig. 1.—*A*, Long sigmoid; *B*, physiologic volvulus; *C*, axial torsion of the rectal loop of the sigmoid in 180 degree volvulus without strangulation of the vessels; *D*, 360 degree volvulus of the sigmoid with beginning strangulation; *E*, 360 degree volvulus of the sigmoid with torsion and strangulation.

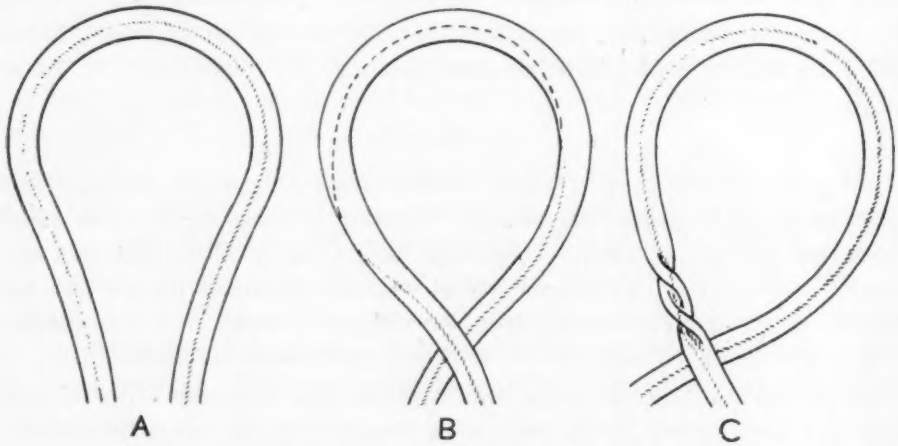

Fig. 2.—Development of torsion stenosis. (From Laurell.)

than 360 degrees is comparatively rare because a torsion of 360 degrees causes so marked a distension of the flexure that it limits itself, and further twisting becomes impossible.

Seventeen of the Ullevaal patients operated upon or examined post mortem showed the degrees of torsion listed in Table II.

TABLE II

NUMBER OF CASES	DEGREES
1	540
6	360
1	270
9	180

Hugo Laurell's assistant, Karl E. Groth, has demonstrated a condition characteristic of a volvulus which produces symptoms, particularly when there is a moderate twisting of the mesentery, that is, volvulus of approximately 180 degrees.

Groth showed that every torsion of the sigmoid and its mesenteric axis is combined with an axial torsion of the bowel itself because the end of the sigmoid is more or less fixed to the posterior peritoneal wall. This axial torsion is twice as great as the torsion of the mesentery. The axial torsion is thus 360 degrees in a 180 degree volvulus. To what extent the axial torsion causes stenosis depends on whether it is evenly distributed throughout the entire sigmoid flexure or is limited to one or more short lengths of the loop. A stenosis of the type designated by Laurell as torsion stenosis occurs where the torsion is concentrated at the points of attachment of the loop, particularly where part or all of the torsion is localized at one side of the loop's vertex. This takes place when the twisted loop is distended with gas. Axial torsion then is forced along until it comes to a fixed part of the bowel. A kink torsion may occur if there is unequal filling of the sigmoid flexure.

The twisting at the axis of the mesentery and the axial torsion about the axis of the bowel which are characteristic of volvulus cause a mechanical ileus in most cases. In those cases in which the torsion is moderate a simple obstruction results. The most important pathologic changes are then caused by distention of the bowel and obstruction. The increased peristalsis seen in these patients forces air and fluid into the twisted sigmoid loop because the site of the torsion acts as a valve which allows air to enter but not to escape. This explains the rapidly developing meteorism in the sigmoid loop. Occasionally the bowel contents may be forced into the efferent loop, so that diarrhea may occur in spite of the other symptoms of occlusion.

When volvulus causes a simple obstruction, the bowel wall remains adequately nourished for the first few days. This is a result of the fact that the sigmoid colon is the part of the intestinal tract that tolerates the highest pressure before blood circulation in the wall stops, and, therefore, is most resistant to the increasing intestinal pressure. Investigators seek the cause of this condition in the different courses of the vessels, in the muscular wall, in the different parts of the intestinal tract.

At operation during the early stages the serosa of the sigmoid is found to be smooth and glistening, and the mucous membrane does not show evidence of any ulceration. In the later stages these cases also show damaged mucous membrane with ulceration and perforation as a result of the torsion and disturbed circulation.

The situation is more serious in the cases in which the volvulus produces a strangulation ileus. As the strangulation increases, the veins are increasingly closed off, and venous stasis occurs. The changes found in the bowel are in direct proportion to the degree of disturbance in the circulation. Sooner or later, depending on the degree of the torsion, thrombosis of the mesentery sets in and spreads. The strangulated loop becomes gangrenous, capillary or larger perforations occur, and peritonitis develops. Usually three or four days elapse before the infarction of the bowel wall becomes so marked that peritonitis develops, but in the most marked strangulations in which the arteries are occluded, a much more rapid development of the pathologic changes may be seen. It is important to bear in mind the changes which take place at the site of torsion. In volvulus with simple obstruction these are more marked at the site of torsion than are the changes seen in the remainder of the sigmoid loop.

After the detorsion of the sigmoid colon, perforation at the site of the torsion may occur and have a fatal outcome. Increased peristalsis, meteorism, and accumulation of fluid soon appear in the prestenotic loop of the colon. Distention is most marked where there is a "closed loop," that is, in instances in which the ileocecal sphincter functions. Exudation in the peritoneal cavity is common in volvulus of the sigmoid flexure. In the Ullevaal study this was found at x-ray examination in two-thirds of the cases. The exudate is yellow and serous in cases of obturation. Peritonitic exudate with a fecal odor is a sign of grave changes in the sigmoid loop. In volvulus of the sigmoid with a functioning ileocecal valve the small bowel continues to have normal function for some time, and the fluid and electrolyte losses are therefore moderate. In more serious forms of volvulus there is fluid and electrolyte loss resulting from formation of ascites, hemorrhage, and vomiting.

THE DISEASE HISTORY

The disease history in volvulus of the sigmoid has several characteristic symptoms which may be explained on the basis of pathologic changes. The first and most important point is the change from normal bowel evacuation, usually a long-continued or periodic constipation. The stools may be bloody or, at times, foul smelling. A report of passing attacks of acute abdominal pain is common. After several milder attacks the patient suddenly has a severe acute attack which makes hospitalization necessary.

A volvulus attack that brings the patient into a hospital may show great variation in its initial symptoms. Some patients report that for several weeks previous to the attack they have noticed a marked decrease in passage of stool and flatus simultaneous with increasing gaseous distention of the abdomen. In other cases the patient may notice a marked sudden stoppage of stool and

flatus, but aside from a noticeable desire for evacuation which he cannot satisfy, one or more days may pass before he has severe symptoms from the sigmoid volvulus, mainly pain, which brings him to the physician.

There are also patients who report milder cramping pain often localized around the umbilicus and accompanied by rumbling in the abdomen and sometimes liquid stools. The intensity of the pain increases rapidly after the onset as a rule.

Fig. 3.—Characteristic contours of the rectum in torsion stenosis.

The number of days from the onset of the symptoms to the admission into the hospital was quite variable in the Ullevaal study. In most cases the patients reported having had symptoms from twelve to seventy-two hours, but in a few cases the duration of the symptoms was as long as ten days or more. A few patients reported that they had not noticed any cessation in the passage of flatus or stool.

As a whole the patients with volvulus of the sigmoid on admission to the hospital appeared less affected than patients with ileus from other causes. Among the 91 patients admitted to Ullevaal a total of 168 times, there were only 21 admissions in which the general condition of the patient was poor. However, patients with acute marked strangulation may present a picture of

deep shock in the course of the first day of the disease. Three of the Ullevaal patients died during the first day of the attack. Post-mortem examination in these patients showed marked gangrene of the sigmoid loop.

The acute pain is characteristic of volvulus. The pain is continuous, indicating a pull on the mesentery, but it is interrupted by colicky pain which is the result of hyperperistalsis. The pains are diffuse without radiation, but they have a tendency to be most marked around the umbilicus.

Inspection of the abdomen shows balloonlike distention localized chiefly to the epigastrium, umbilical region, and left hypochondrium. The outline of the loops may often be seen. It is noteworthy that in the large number of cases in the Ullevaal study only four patients were described as having an abdomen with a normal-appearing contour. In seven cases the abdomen was described as somewhat distended, while in the remainder of the cases there was marked distention, which thus is seen to be a fairly constant symptom of volvulus of the sigmoid. Auscultation of the abdomen is of great importance. Except in enteritis, fluid sounds (gurgle sounds) are a constant finding in ileus. They were found in almost all cases in the Ullevaal study of volvulus of the sigmoid. Marked tenderness and muscular resistance are rare and are symptomatic of a bowel lesion with peritonitis. Vomiting occurs as a reflex at the onset, but later vomiting is rare and indicates complications. Digital examination of the rectum shows a large empty ampulla. The site of the torsion is too high for palpation per rectum, but occasionally a certain amount of resistance can be felt. Fever occurs only in complicated cases. Laboratory examinations required for the necessary supportive treatment are in order, but such examinations do not offer any special help in diagnosis.

X-RAY EXAMINATION

The x-ray examination, which is of great importance in both diagnosis and treatment, should be done in all cases in which there is a suspicion of volvulus. This was carried out routinely by the x-ray department at Ullevaal.

X-rays of acute volvulus of the sigmoid reveal some of the following findings:

1. A more or less markedly distended sigmoid.
2. Fluid levels in the sigmoid loop with little difference in levels in erect position. (This symptom was absent in one of sixty patients examined the last years at Ullevaal.)
3. Moderate gaseous and fluid distention of the remainder of the colon. (Absent in one of our sixty cases.)
4. Balloonlike distention of the cecum rare and seen chiefly in peritonitis. (Such distention was observed in one of our sixty cases.)
5. Gas in the small bowel rare and seen chiefly in peritonitis. (It was found in nine of the sixty cases.)
6. Spiral patterns on the mucous membrane at the site of torsion. This occurred only when the torsion was limited to a small segment of the bowel.

7. Thickened but smooth walls in the sigmoid flexure.
8. Domes of the diaphragm high and almost rigid.
9. Fluid in the peritoneal cavity. This occurred with progressive compromise of the circulation of the torsioned sigmoid.
10. Signs of peritonitis in strangulation with gangrene as suggested in the presence of fluid between the distended intestinal coils.
11. Barium enema demonstrating a characteristic outline of the proximal part of the rectum, a bird's-bill shape with spiral narrowing. The sharply cut off margin, as is observed in cancer, is never seen in volvulus.

In atypical cases the diagnosis is difficult, and the examiner may make mistakes. An x-ray check on the effect of treatment is of the greatest aid.

TREATMENT

The treatment may be either nonoperative or operative. There is a possibility that spontaneous untwisting of the sigmoid exists when the torsion is less than 360 degrees. In torsion of 360 degrees or more the twisted loop is usually held fast between the anterior and posterior abdominal wall.

In the Ullevaal study the volvulus condition was repaired spontaneously in only three cases after the patient was admitted to the hospital. Many of the case histories suggest that a spontaneous reposition of the volvulus is common. However, it is difficult to determine when the conditions for such repair are present. An ordinary enema may be followed by detorsion if the degree of torsion is moderate. The effect is often uncertain and temporary, and it is difficult to be certain that the volvulus has been completely untwisted. In the Ullevaal study detorsion occurred twice after an ordinary enema. A better and more easily controlled method is an attempt at reposition by means of a barium enema during fluoroscopy. Nörgaard has described successful reposition by this method. It was not used routinely at the Ullevaal, but volvulus was twice repaired during examination with a barium enema.

The chief obstacle to reduction of the torsioned and distended sigmoid loop is that the loop usually fastens itself because of its size, thus hindering the bowel's own attempt at untwisting. It is reasonable to suppose that a spontaneous reduction could take place if one emptied the bowel. The axial torsion would not then be forced into a limited part of the sigmoid but could be divided over a larger area, thus allowing spontaneous detorsion to take place. A number of investigators have described the immediate detorsion of the volvulus which takes place when a tube is inserted past the site of the torsion. The prerequisite for carrying out such treatment, consisting of inserting a tube or other hollow instrument past the site of torsion, is that there is no danger of injury, particularly of perforation at the site of torsion. This latter method has been used in the treatment of volvulus of the sigmoid at Ullevaal hospital in most cases with good results, as I shall relate later.

The simplest means of emptying the sigmoid flexure is to insert a tube per rectum past the stricture. This method has some drawbacks. It is necessary

to use a fairly soft tube to avoid the danger of perforation, and a soft tube may easily curl back upon itself instead of passing the site of occlusion because it would be only the merest chance that a tube could find its way past the obstruction.

In the Ullevaal study reduction by means of a tube was accomplished in five cases with good results. Some patients have employed such treatment themselves. A 64-year-old man reported that in the course of the last twenty years he had regularly used a tube 7 mm. in diameter and 60 cm. long as soon as he noticed any distention. In this way he relieved both the distention and the pain, at least once a week and sometimes daily.

Experience has shown that it is much easier to guide the tube past the point of torsion if it is inserted through a proctoscope so that the field may be seen. After the surgeon has been informed by the roentgenologist as to the degree of occlusion and the direction of the bowel, he may insert the proctoscope as far as the site of torsion with the aid of careful inflation of the rectum. The site is easily recognized by the spiral folds seen there. Proctoscopic examination provides the examiner with an impression of the condition of the bowel, the appearance of the mucous membrane, and the blood supply at the site of torsion. In some cases the appearance of the mucous membrane may be such that the examiner considers it risky to insert the tube.

When the site of torsion has been located, a lubricated rubber rectal tube 60 cm. long and about the thickness of a finger is guided up past the site of obstruction. Force must not be used, but the tube usually slips into place without trouble. In some cases the proctoscope has been inserted past the site of torsion before passing the tube, but the method first described is considered the best. There is very seldom doubt whether the treatment has succeeded because a forceful evacuation of flatus and thin stool is immediate, and the patient feels instant relief. The result may be verified by x-ray examination.

Usually the torsion of the sigmoid is between 15 and 25 cm. from the anus. In the Ullevaal study, the proctoscope was inserted more than 30 cm. before coming to the site of torsion in only six cases. At Ullevaal where proctoscopy with the use of the tube has been the routine method of treatment for volvulus of the sigmoid for several years, the method was followed by an immediate satisfactory result in a total of 123 trials in the period from 1936 to 1946.

In judging the reduction of the volvulus by this means as satisfactory, there is one reservation necessary: that although the method is effective in the treatment of the acute attack it has no effect on the marked tendency to recurrence. This tendency was not infrequent among the patients referred to previously. When the tube slipped out soon after the reduction of the volvulus, recurrence was noted within a few hours in some patients. Therefore it is necessary that the tube remain in place two or three days after reduction. The tube should be sewn to the anal ring. The patient should be observed very closely the first few days after the treatment.

I have heard surgeons warn against the method which I have just discussed because of the danger of perforation and because one might fail to operate on patients with strangulation and gangrene. I believe that the Ullevaal study

is a strong argument against such warning. That such warning cannot be entirely ignored should be an added incentive for caution to those using the method. The method must not be used when the clinical examination leaves some doubt as to whether there are serious circulatory changes in the bowel, either at the site of torsion or elsewhere.

In one case the bowel was perforated during insertion of the tube after proctoscopy. A laparotomy was done, but the patient, a 71-year-old man, died. Three patients died in spite of treatment with proctoscopy and intubation of the obstructed sigmoid, but not because of the treatment. All three patients were in poor condition upon admission and died after a few days. No signs of volvulus of the sigmoid or gangrene were found at the post-mortem examination.

Proctoscopy and attempts at intubation were unsuccessful nine times. These patients were operated upon immediately afterward. The previous treatment had no untoward effect in so far as could be determined. In a very few patients the method was not used because clinical and x-ray findings contraindicated its use. Two patients were in such poor condition at the time of admission that they died about one-half hour after arrival, before any treatment was begun.

This treatment should perhaps be credited with a fatality in one case in which there was no volvulus. The patient was an 80-year-old man who was treated with proctoscopy and intubation after the condition was diagnosed as volvulus of the sigmoid. When the treatment failed to produce the desired effect and because of the onset of symptoms of peritoneal irritation, laparotomy was performed the next day. The distal part of the sigmoid was found to be constricted by a strangulating band. There was no perforation and no volvulus. Division with closure of the distal segment of the sigmoid and exteriorization of the proximal part was done. The patient died of an intraperitoneal hemorrhage the next day.

A mortality of 4 in 136 treatments is to be considered a satisfactory result. The drawback of the method is that it is not a definitive treatment. The tendency to recurrence is great, and these patients are in and out of the hospital many times in the course of a few years. Thirty-one of the Ullevaal patients were admitted to the department two or more times for the disease. However, they are older people, many of them aged, who run a considerable risk from radical operative treatment.

OPERATIVE TREATMENT

In those cases in which treatment with proctoscopy and passage of a tube could not be done because serious bowel damage could not be ruled out, or in which the treatment was not successful, laparotomy was done. The simplest and, according to our experience, correct operative procedure is laparotomy accompanied by insertion of a tube per rectum and detorsion. In order to do this safely there must be no gangrene at the site of torsion nor any other serious bowel damage. I believe it is correct to insert a tube, controlling its passage by placing a hand in the peritoneal cavity as soon as the abdomen is opened,

and to delay the risky reposition of the distended sigmoid flexure until the flatus and fluid have been removed. If there is gangrene the loop should be lifted out of the peritoneal cavity and punctured. In the cases in which there is gangrene of the sigmoid loop, bowel resection should be done.

Because the site of torsion is so distal in the sigmoid flexure a Mikulicz exteriorization resection cannot be employed in most instances, because there is some risk of producing too much pull on the efferent loop of the sigmoid colon, which may cause gangrene and peritonitis. The operative treatment should be carried out in such a manner that after resection of the gangrenous part of the sigmoid, the distal stump is inverted and buried. Then the proximal part is brought out as a colostomy opening. An anastomosis between the proximal and distal parts of the sigmoid may be made at a later laparotomy.

Eighteen patients were operated upon during the acute stage in the Ullevaal study. Ten patients were treated with laparotomy and detorsion. One of the latter died as the result of peritonitis which developed from a distention perforation of the cecum. One patient had a primary resection of the colon with a satisfactory result. One patient had a sigmoidostomy with a satisfactory result. One patient was treated with cecostomy after a wrong diagnosis of cancer of the sigmoid was made. This patient did not have x-ray examination with a barium enema because the roentgenologist thought the risk was too great. The patient died.

Sigmoidostomy and cecostomy have no place in the treatment of volvulus of the sigmoid. Resection of the sigmoid colon with exterioration by the method of Mikulicz was done in five cases. One of these patients was referred to before. In this case perforation occurred after insertion of the tube. In two cases pneumoperitoneum and peritonitis resulting from perforation of gangrenous bowel loop were found at operation. The fourth patient, an 87-year-old man, was found to have a completely gangrenous sigmoid flexure. All these patients died. The fifth patient did not die as the result of the exteriorization resection, but in connection with the closure of the sigmoid fistula.

RESULTS OF CONSERVATIVE AND OPERATIVE REDUCTION

The collected results of the treatment of acute volvulus of the sigmoid at the surgical departments of Ullevaal hospital give the figures listed in Table III.

TABLE III

KIND OF TREATMENT	NUMBER OF TREATMENTS	DIED
None	2	2
Spontaneous reduction	3	
Reduction by enema	2	
Reduction with a barium enema	2	
Reduction with a rectal tube	5	
Reduction with proctoscopy and rectal tube	136	4
Laparotomy and detorsion	10	1
Laparotomy and cecostomy	1	1
Laparotomy and sigmoidostomy	1	
Laparotomy and primary resection	1	
Laparotomy and exteriorization resection	5	5
Total	168	13

The mortality rate for the 168 treatments is thus 7.7 per cent. The mortality rate for the 91 patients treated is 14.2 per cent. This is a satisfactory rate considering the circumstance that most of the patients were old, many exhibiting the mental deterioration accompanying senility. Moreover, the physical condition of many of the patients was poor.

From many clinics in which operative treatment is used exclusively the mortality rate is reported to be as high as 30 to 60 per cent. Radical removal of the sigmoid which has undergone repeated torsions may be carried out with small fatal risk during the symptom-free interval. At Ullevaal, Surgical Department III, the method used was resection of the enlarged sigmoid loop in several stages: (1) cecostomy, (2) exteriorization resection by the Mikulicz

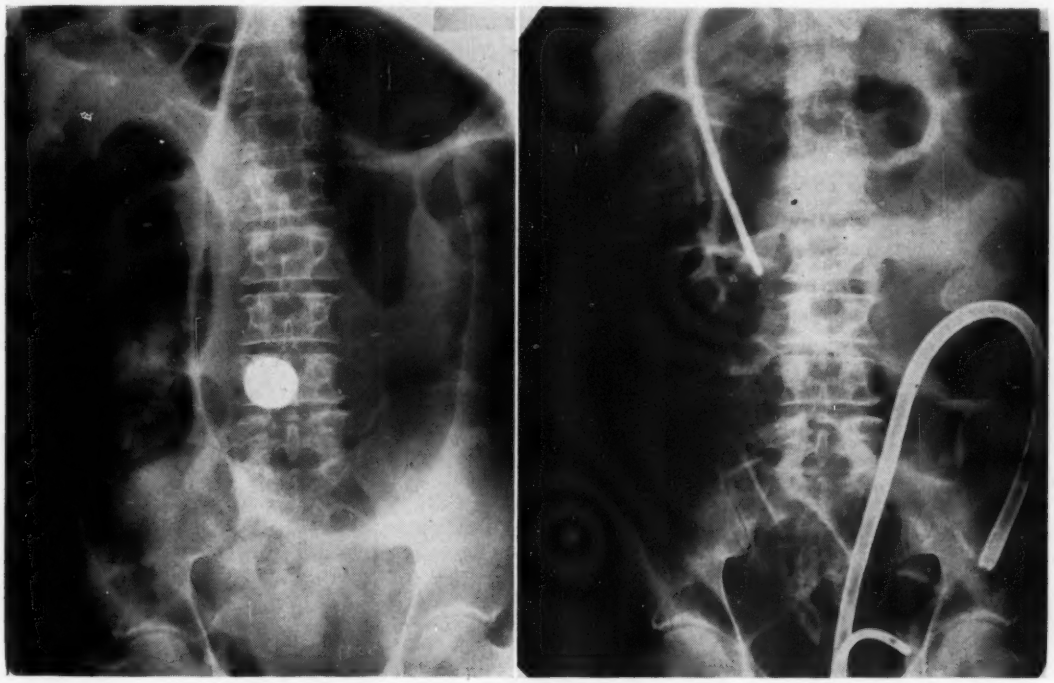

Fig. 4.—Volvulus of the sigmoid before and after reduction with proctoscopy and intubation. (From University of Minnesota Hospitals.)

method, (3) closure of the sigmoidostomy, (4) closure of the cecostomy. In the ten-year period from 1936 to 1946 this procedure was carried out seven times. The results were satisfactory in all cases. This four-stage operation will in most cases keep the patient in the hospital for three to four months.

During my stay at the Minnesota University Hospitals from January to May, 1947, I had the opportunity to see two cases of volvulus of the sigmoid reduced with proctoscopy and intubation. In two patients Wangensteen performed a primary resection of the sigmoid about fourteen days after the acute volvulus had been reduced. Both patients were discharged from the hospital in good condition about one week after the operation. In treating patients with repeated attacks of volvulus in the free period of the disease, a closed resection

of the sigmoid combined with intestinal suction through a nasal tube the first day after the operation, as performed in Wangensteen's clinic, seems to be a better method than the four-stage operation used in Ullevaal.

SUMMARY

A 10-year study is discussed of volvulus of the sigmoid from the surgical departments at the Ullevaal Hospital, Oslo. The study includes 91 patients admitted to the hospital 168 times. The experience from this material demonstrates that in most cases of volvulus of the sigmoid there is a torsion of the sigmoid with obstruction of the lumen, but no strangulation and no serious circulatory disturbances in the sigmoid.

In those cases in which the clinical examination did not give evidence of serious circulatory disturbances in the sigmoid treatment consisting of proctoscopy and intubation with a rectal tube 60 cm. long and 6 to 10 mm. in diameter was used. This treatment was used 123 times without complications. Three patients (in poor condition on admission) died in spite of apparently successful treatment, and one patient died after instrumental perforation. In nine cases attempts at intubation by proctoscopy were unsuccessful, but did no harm to the patients. These patients had to be operated upon immediately afterward. Eighteen patients were operated upon during the acute stage in the Ullevaal study. The operation in the acute stage must be conservative if possible.

The 91 patients in the study were admitted to the hospital 168 times. The mortality for the 168 treatments was 7.7. The mortality for the 91 patients was 14.2.

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ACUTE DIVERTICULITIS OF THE CECUM

Study of Ninety-Nine Surgical Cases

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DIVERTICULA of the cecum are usually considered rare. Ochsner and Bargen[1] reviewed 151 cases of uncomplicated diverticulosis of the colon and found that in about 2 per cent of the cases the diverticula occurred in the right half of the colon. When diverticula or outpouchings occur in the intestine without inflammation, the term diverticulosis is applied, while if inflammation with or without obstruction occurs, the term diverticulitis is used.

The incidence of diverticula of the colon in the general population is difficult to evaluate. In 31,838 roentgenologic examinations of the colon done at the Mayo Clinic it was found that 5.7 per cent of the patients examined had colonic diverticula. However, in 6.9 per cent of cases in which necropsy was performed during one year at the clinic, diverticula of the large bowel were observed.

The incidence of diverticulitis is also difficult to evaluate. Ochsner and Bargen stated that about 14 per cent of diverticula become inflamed. In about 15 per cent of cases of diverticulitis operation is performed.

Although diverticula may be found in any portion of the large bowel between the ileocecal valve and the rectum, the sigmoid is the most common site. The reason for this fact is not entirely clear but the distribution of diverticula may be due to the difference in the consistency of the fecal column. In the right portion of the colon it is liquid, but in the left portion its formed, solid nature makes it possible for fecaliths to exert pressure on the potential hernial areas. At these points blood vessels pierce the muscular coat of the intestinal wall and thus leave weakened sites where the mucosa, by protruding through, may form so-called false diverticula.

In many discussions of diverticulitis a clear distinction between acute and chronic diverticulitis is not made. For our purposes we shall consider that cases in which there were symptoms of sufficient severity to cause operation to be performed, coupled with the finding of enough pathologic changes in a cecal diverticulum to explain those symptoms, are cases of acute diverticulitis of the cecum.

We were unable to find any articles giving a complete review of the literature on acute diverticulitis of the cecum. In 1937, Bennett-Jones[2] reported twenty cases from the English literature. Five years later Busch and Friedfeld[3] reviewed a total of twenty-seven cases while adding a case of their own. In 1943, Baker and Carlile[4] summarized thirty-seven cases and added two from their own experience.

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We were able to find in the literature reports of ninety-one cases of acute diverticulitis of the cecum. Of some 700 cases of surgical diverticulitis of the colon at the Mayo Clinic, only nine seemed to be relatively acute surgical problems involving the cecum only.

REPORT OF CASES FROM MAYO CLINIC

CASE 1.—The patient was a girl, 16 years of age. Five days before coming to the clinic she had complained of generalized abdominal cramps, vomiting, and fever. On examination she seemed to have a fullness in the right iliac fossa. Five days after admission to the hospital, as it was felt that the abscess was localized, it was surgically drained. The appendix was not removed. Two split rubber tubes were inserted for drainage. The patient was dismissed from the hospital in twenty-four days, at which time drainage persisted. Three months later the appendix was removed and a large opening in the cecum, which seemed to connect with the fistula, was closed. The patient was dismissed from the hospital in fifteen days. The fistula persisted for one and one-half years and then closed spontaneously. Twenty years after the original visit the patient returned to the clinic complaining of a tender scar, especially so in the past two months. During this time she complained of pain and swelling in the region of the scar, which she could partially relieve by pressure over the swelling. Operation was advised and at exploration an inflamed diverticulum of the cecum, containing a large fecalith, was found, extending up to the undersurface of the anterior abdominal wall. It was possible to free the adhesions about the neck of the diverticulum and invaginate the entire sac into the lumen of the cecum. The base was closed with two rows of sutures. The incision healed without incident and the patient was dismissed from the hospital on the twelfth postoperative day. She returned to the clinic fourteen years after this last operation, or thirty-four years after the first operation, with no complaints relative to the gastrointestinal tract.

CASE 2.—The patient was a woman, 30 years of age. For eight years before coming to the clinic, she had been having intermittent attacks of pain in the right lower quadrant of the abdomen. These attacks had become more frequent in the past year, the last one starting forty-eight hours before admission. Constipation and flatulence were always associated with the attacks. On examination there was observed a tender movable mass about 7 cm. in diameter in the lower right quadrant of the abdomen, which seemed to be contiguous to the right adnexa. At operation, the right ovary and tube were found to be involved in a mass which was attached to an inflamed diverticulum of the cecum. The diverticulum was about 1½ inches (3.8 cm.) in length and was situated about 1½ inches (3.8 cm.) from the base of the appendix. Right salpingo-oophorectomy, appendectomy, and diverticulectomy were performed, the entire mass being removed together. The opening into the cecum was closed with linen sutures. The patient was dismissed from the hospital on the seventeenth postoperative day. She returned to the clinic eight months later. At this time she felt well.

CASE 3.—The patient was a woman 24 years of age. Eight years previous to admission to the clinic, she had had an attack of pain in the right lower quadrant and the appendix had been removed. In the intervening eight years she had suffered from a stabbing pain in the region of the wound and soreness there from time to time. Six weeks before admission well-marked persistent leucorrhea, associated with daily morning diarrhea, had developed. On examination there were considerable thickening and tenderness of the ascending colon. The patient was not inclined to undergo further examination and left the clinic.

Eight months later she returned, having been ill for four days. Temperature was slightly elevated and the abdominal wall over the right iliac fossa was exquisitely tender. The tenderness was perceptible by both rectal and vaginal examination and a small mass was palpable near the cecum. She stated that "pus" had been draining from the rectum in the previous few days. Because of the relatively acute nature of the case, operation

was performed immediately. The uterus was found to be retroverted but the tubes and ovaries seemed normal. There was an inflamed diverticulum, measuring 2 by 4 cm., near the base of the old appendical scar, around which there were many adhesions. It was freed and inverted into the cecum and the base was closed with two rows of chromic catgut. The incision was closed without drainage and the patient was dismissed from the hospital in two weeks. She was seen at the clinic five years later complaining of asthmatic bronchitis. There was no reference to any intra-abdominal trouble.

CASE 4.—The patient was a woman, 40 years of age. She stated that two years before coming to the clinic, she had had a pelvic operation in which a cystic mass, interpreted as ovarian in origin, had been drained. The incision had never completely healed. She stated that there was daily discharge from a small sinus but that it was not foul or fecal in nature. Five days previous to coming to the clinic she had become ill, with nausea, vomiting, and obstipation. The right lower quadrant of the abdomen had been very painful. She was sent directly to the hospital and, when examined there, was found to have a draining sinus from an old lower midline scar, with an egg-sized mass just above the inguinal ligament, which was very tender. Leucocytes numbered 9,900 per cubic millimeter of blood. The preoperative diagnosis was draining abdominal sinus with possible adjacent abscess.

Using a secondary midline incision, the sinus tract was dissected down to a region between a small cystic right ovary and a large inflamed diverticulum of the cecum, both surrounded by a mass of adhesions and lying in a matted mass of small bowel. The organs were partially separated and the diverticulum was freed at its base, ligated, and cut. The base was inverted into the lumen of the cecum and closed with a purse-string suture. Subtotal hysterectomy, right salpingo-oophorectomy, and diverticulectomy were performed, the whole being removed in one mass.

Unfortunately, the abdominal sinus persisted and a secondary operation was necessary six months later, at which time the sinus tract was successfully removed. The patient has since remained well.

CASE 5.—The patient was a man, 44 years of age. Shortly before he came to the clinic, severe bronchitis and numerous bouts of severe coughing developed. About ten days before coming, he awoke one night coughing severely and noted that the abdomen was greatly distended and that there was considerable distress in the right lower quadrant. When he visited his physician a mass was found in the right lower quadrant. When he was examined at the clinic a mass was noted which seemed to be about the size of a pigeon's egg and fairly movable. A roentgenogram of the colon showed multiple diverticula of the entire large bowel with a mass in the region of the cecum which seemed to be extrinsic and posterior to the bowel. Leucocytes numbered 9,500 per cubic millimeter of blood and examination of the urine gave negative results. At operation the tumor proved to be a perforated, walled-off diverticulum of the cecum. The pocket of the diverticulum was opened and the opening into the cecum was closed with chromic catgut and silk. The wall of the diverticulum was excised and the appendix was removed. The postoperative course was uneventful, the wound healed without drainage, and the patient was dismissed from the hospital on the twenty-first day. When he returned to the clinic ten years later, his only complaint was from the headaches associated with severe hypertension.

CASE 6.—The patient was a woman, 45 years of age. She had suffered from several attacks of indigestion in the year before she came to the clinic. She had pain in the right lower quadrant of the abdomen, associated with constipation. Examination at the clinic had just started when she complained of pain in the right lower quadrant. Tenderness was noted over the cecum and right adnexa. Leucocytes numbered 14,700 per cubic millimeter of blood with 90 per cent polymorphonuclear leucocytes. A diagnosis of appendicitis was made and exploration was performed. When the peritoneum was opened, there was considerable exudate and muddy fluid about the cecum and pelvis. The appendix was removed. As the cecum was lifted up, there appeared several small diverticula on its

lateral and posterior surface, one of which was severely inflamed and necrotic but did not seem to be perforated. The diverticula were not removed. Ten grams of sulfathiazole were placed over the region and the abdomen was closed without drainage. The pathologist reported chronic appendicitis with subacute periappendicitis. The postoperative course was uneventful and the patient was dismissed on the thirteenth day. She was put on a low residue diet and has had no return of the attacks, except for occasional burning sensation with bowel movements.

CASE 7.—The patient was a man, 48 years of age. The most acute attack of diverticulitis had come three weeks before he visited the clinic. He had been seized with sudden, severe, colicky pain in the right side and his physician had noted a large tender mass in the right lower quadrant. The mass had partially resolved under conservative treatment with the use of mineral oil and heat. Intravenous urograms made by his physician were said to have been negative.

On examination at the clinic the patient's abdomen showed a scar in the right upper quadrant from cholecystectomy and appendectomy, which he stated had been done three years before. In the right lower quadrant was a mass the size of an orange, freely movable. It was only slightly tender. Roentgenologic examination of the colon showed multiple diverticula of the cecum associated with an extrinsic or intrinsic mass near the ileocecal valve. Leucocytes numbered 8,600 per cubic millimeter of blood.

Operation revealed a perforating lesion of the cecum which was firmly adherent to the anterior abdominal wall, forming an indurated mass measuring 4 by 5 cm. Attached to the mass were numerous loops of small bowel. Ileotransversostomy was performed. The ileum was divided about ten inches (25 cm.) from the ileocecal valve, both ends were turned in, and a side-to-side anastomosis was made between the proximal end of the ileum and the right half of the transverse colon. It was hoped that the mass would disappear when the fecal stream was thus by-passed. Five grams of sulfathiazole were inserted into the peritoneal cavity and the incision was closed without drainage.

The patient got along fairly well for three months but the mass persisted. He reregistered at the clinic later and right colectomy was performed. The pathologist reported that at the junction of the cecum and ascending colon there were multiple small diverticula (diverticulosis). One of these diverticula had perforated, forming a pericecal inflammatory mass 4 by 4 by 3 cm. (diverticulitis). The patient had a second uneventful postoperative course and was dismissed from the hospital on the thirteenth postoperative day.

CASE 8.—The patient, a man 40 years of age, was admitted directly to the hospital complaining of a low-grade ache in the right lower quadrant, which had been present the previous thirty hours. He had not had any major gastrointestinal symptoms previous to that time. Five hours before admission the pain had become much more severe and was described as being colicky. Leucocytes numbered 13,700 per cubic millimeter of blood with 85 per cent polymorphonuclear leucocytes. Examination of the urine gave negative results. On physical examination the entire right side of the abdomen was found to be very tender and rigid. A diagnosis of acute appendicitis was made and operation was performed. When the peritoneum was opened through a right rectus incision, thick purulent fluid was noted in the right lower quadrant. There was also a considerable inflammatory reaction around the cecum. The appendix did not seem greatly inflamed but it was removed. When a piece of fat over the lower anterior wall of the cecum was lifted a fecalith was found to be protruding through the end of a small, acutely inflamed diverticulum. The fecalith was pushed into the lumen of the bowel, the diverticulum was inverted into the cecum, and the opening was closed with a chromic catgut suture. A piece of fat was sutured over this. Exploration of the colon did not reveal any other diverticula. The sigmoid was palpated for the presence of diverticula but none were felt. Ten grams of sulfathiazole were inserted intraperitoneally and 5 Gm. of sulfanilamide were placed in the incision.

The postoperative course was uneventful, the patient being dismissed from the hospital on the thirteenth day.

TABLE I. DATA ON CASES OF ACUTE DIVERTICULITIS OF THE CECUM REPORTED IN THE LITERATURE

AUTHOR	YEAR	AGE (YR.)	SEX	GROSS APPEARANCE AT OPERATION	OPERATION
Bagetti[5]	1941	32	M	Tumor size of Brazil nut	Ileocecal resection*
Baker and Carlile[4]	1943	34	M	Mass involving entire cecum	Cecectomy with ileotransverse colostomy*
Baker and Carlile[4]	1943	59	M	Inflamed mass 1.5 cm. from appendix	Excision and closure*
Barbier[6]	1938	45	F	Perforating tumor	Inverted with purse-string suture*
Bearse[7]	1939	19	F	Mass size of tennis ball, top of cecum, full of pus	Drained; x-ray view later showed single diverticulum*
Bennett-Jones[2]	1937	21	F	Mass 1.5 cm. diameter, anterior aspect of cecum	Excision and closure in layers*
Bennett-Jones[2]	1937	28	F	Mass, anterior aspect of cecum	Excision and closure in layers*
Bennett-Jones[2]	1937	26	M	Mass, posterolateral surface of cecum	Right colectomy with end-to-side anastomosis*
Bryan[8]	1930	28	F	Large irregular mass lateral to cecum	Cecectomy*
Bryan[8]	1930	30	M	Numerous small inflamed masses in cecum	Right colectomy*
Burgess[9]	1940	42	F	Small inflamed diverticulum	Diverticulectomy and appendectomy*
Burgess[9]	1940	30	F	Lateral inflamed mass	Excision and closure*
Burgess[9]	1940	60	F	Mass size of hen's egg	Excision and closure*
Burgess[9]	1940	22	F	Inflamed diverticulum	Appendectomy and drainage*
Busch and Friedfeld[3]	1942	25	F	2.5 cm. mass on lateral side of cecum	Excision and closure*
Carroll[10]	1943	56	F	Mass 5 cm. above junction of ileum and cecum	Right colectomy*
Conway and Hitzrot[11]	1931	44	F	Mass size of two fists involving cecum	Right colectomy†
Conway and Hitzrot[11]	1931	32	M	Perforating diverticulum near valve with peritonitis	Diverticulectomy†
Conway and Hitzrot[11]	1931	53	M	Diverticulum of lower lateral cecum	Diverticulectomy*
Cooke[12]	1922	51	M	Not stated	Cecectomy*
Dalger and Coureaud[13]	1927	20	M	Posterolateral perforation, but the neck of the diverticulum did not connect with the lumen of the cecum	Appendectomy and diverticulectomy*
D'Argen court[14]	1944	35	F	Anterior, 7.6 cm. diameter	Diverticulectomy and appendectomy*
Delitala[15]	1939	42	M	Hazelnut-sized mass near appendix	Excision and closure*
Doppler[16]	1936	?	?	Tumor anterior cecum	Ileocecal resection‡
Epstein[17]	1933	62	F	Mass near cecum	Excision and inversion*
Fasano[18]	1937	34	M	Anterolateral tumor	Inverted diverticulum and closed*
Fifield[19]	1927	?	?	Mass over cecum	Ligated and removed*
Fifield[19]	1927	?	?	Mass over cecum	Ligated and removed*
Fifield[19]	1927	?	?	Mass over cecum	Ligated and removed*
Fossati[20]	1942	53	M	Egg-sized tumor, high on lateral wall	Right colectomy*

(Table I continued on following pages.)

TABLE I—CONT'D

AUTHOR	YEAR	AGE (YR.)	SEX	GROSS APPEARANCE AT OPERATION	OPERATION
Freeman[21]	1927	40	M	Congested diverticulum just above valve	Diverticulectomy*
Frehling[22]	1933	51	F	Smooth lateral mass	Right colectomy*
Frehling[23]	1945	37	M	Mass posterior wall of cecum	Exteriorized; draining sinus developed*
French[24]	1923	29	F	Diverticulum 2 cm. diameter	Excision and closure*
French[24]	1923	62	F	Mass involving cecum	Cecectomy*
Fritz[25]	1943	59	M	Hard mass involving cecum	Right colectomy*
Gant[26]	1921	63	M	Mass looked like tumor	Excised†
Gatewood[27]	1945	30	M	Inflamed mass in antero-medial wall	Diverticulectomy and appendectomy*
Gatewood[27]	1945	21	M	Retroperitoneal mass, size of hen's egg	Diverticulectomy and appendectomy*
Grace[28]	1940	37	F	Anterior mass, size of egg yolk	Diverticulectomy*
Grace[29]	1938	40	M	Posterior mass, size of egg yolk	Right colectomy*
Graves[30]	1938	?	F	Lateral mass 2 cm. diameter	Exteriorized and removed in ten days*
Graves[30]	1938	?	M	6 cm. mass lateral with subacute perforation	Drained; postoperative fistula for one year*
Greensfelder and Hiller[31]	1929	38	F	Traction diverticulum at base	Freed and inverted?*
Greensfelder and Hiller[31]	1929	46	M	Lateral mass, size 1 by 2 cm.	Diverticulectomy*
Hendtlass[32]	1944	17	F	Feces free in abdomen from 1.3 cm. perforation of diverticulum	Diverticulectomy and appendectomy*
Jackson[33]	1917	23	F	Lateral mass 6.4 by 7.6 cm.	Cecectomy‡
Jonas[34]	1940	50	F	?	Excision and inversion*
Jonas[34]	1940	28	F	?	Cecectomy*
Jonas[34]	1940	47	M	?	Excision and inversion*
Jonas[34]	1940	48	F	?	Excision and inversion*
Jonas[34]	1940	36	F	?	Excision and inversion*
Kennon[35]	1933	26	M	Posterior mass 6.3 by 1.3 cm.	?‡
Klages[36]	1937	52	M	2 cm. tumor above appendix	Excised tumor and appendix*
Leonardo[37]	1930	63	F	Superior mass 5 by 3.8 cm.	Diverticulectomy and appendectomy‡
McBee[38]	1940	42	F	Inflamed mass, medial side	Right colectomy*
McBee[38]	1940	32	F	Mass size of egg	Right colectomy*
McVay[39]	1927	36	M	Medial mass 2 by 1.5 cm.	Diverticulectomy and appendectomy*
McWhorter[40]	1934	19	M	Perforating mass, antero-lateral	Closure of neck of diverticulum*
McWhorter[40]	1934	34	M	Lateral mass 1.5 cm. diameter	Excision*
Moschowitz[41]	1918	44	M	Inflamed epiploic tag containing diverticulum	Removal and closure*
Obenour[42]	1938	52	M	Gangrenous mass at junction	Diverticulectomy and appendectomy*
O'Callagham[43]	1937	68	F	Tumor size of child's head	Diverticulectomy*
Owings and Morgan[44]	1940	42	F	Lateral mass as large as hand	Right colectomy*

TABLE I—CONT'D

AUTHOR	YEAR	AGE (YR.)	SEX	GROSS APPEARANCE AT OPERATION	OPERATION
Pereira[45]	1927	54	F	1.3 cm. diverticulum near appendix	Cecectomy*
Pessagno[46]	1935	52	F	Medial border, size of hen's egg	Cecectomy*
Porter[47]	1925	60	F	Lateral mass 2 cm. diameter	Right colectomy§
Potier[48]	1912	32	F	?	Diverticulectomy and appendectomy*
Rogers and Hilton[49]	1930	39	M	Medial mass 2 cm. diameter	Partial cecectomy*
Sammartino and Cervini[50]	1938	66	F	Walled-off abscess behind cecum and generalized peritonitis	Diverticulectomy and appendectomy*
Schnug[51]	1943	30	M	2.5 by 2.5 cm. mass, 3 cm. above valve	Diverticulectomy*
Schnug[51]	1943	59	M	Whole cecum in a mass (inflamed)	Right colectomy*
Schnug[51]	1943	31	M	?	Diverticulectomy*
Schnug[51]	1943	29	M	?	Diverticulectomy and appendectomy*
Schnug[51]	1943	66	F	Pericecal abscess	Drained†
Schnug[51]	1943	47	M	Acute inflamed diverticulum	Appendectomy and diverticulectomy*
Shimizu[52]	1937	49	M	3 cm. mass near valve	Excised*
Staley[53]	1939	56	F	4 cm. mass 1 cm. from appendix	Diverticulectomy*
Stetten[54]	1936	35	F	2 cm. above valve, mass size of thumb	Right colectomy*
Stewart[55]	1930	54	M	Diverticulum 1 by 1.5 cm.	Right colectomy‡
Sumii[56]	1936	57	M	Walnut-sized mass 1 cm. from valve	Ileocecal resection*
Szabó[57]	1937	29	F	Nut-sized mass, anterior cecum	Cecal resection*
Gordon-Taylor[58]	1939	69	M	Lemon-sized mass near valve	Right colectomy†
Thomsen[59]	1935	55	M	Large diverticulum with torsion	Excision*
Thomsen[59]	1935	54	F	Walnut-sized lateral mass	Right colectomy*
Thomsen[59]	1935	23	M	2.5 cm. diameter mass, lateral	?*
Tschudi[60]	1936	54	M	Walnut-sized tumor near valve	Cecectomy†
Walkling[61]	1941	43	M	Mass of inflamed tissue with abscess opening in cecum	Drained abscess‡
Weible[62]	1937	54	F	Apple-sized mass, anterior	Cecectomy*
Weible[62]	1937	35	M	Anterior mass	Closed with purse-string suture*
Wilson[63]	1932	?	?	Inflamed diverticulum of cecum	Diverticulectomy*

*Patient recovered.
†Patient died.
‡Result not stated.
§Patient died from gangrene of the intestine.

ANALYSIS OF DATA

Some data on the ninety-one cases in the literature are shown in Table I. Combining information from these with the eight cases in the clinic records brings out some rather interesting results.

Age.—The average age of all the patients who underwent operation was 39.1 years. The women averaged 41.6 years of age, the men 36.6. This is striking in view of the fact that surgical diverticulitis is usually considered to be a disease which attacks persons past middle age.

Sex.—The sex of the patients was given in ninety-two of the ninety-nine cases. Forty-five were women and forty-seven men. This, too, is unusual since practically all studies of patients on whom operation for diverticulitis has been performed show a heavy preponderance of males.

Operative Mortality Rate.—Of the ninety-four cases in which the outcome of operations was reported, in six it was stated that the patient failed to recover, thus giving an over-all mortality rate of 6.4 per cent. This is considerably lower than the mortality rate in most published series of cases of surgical diverticulitis. In two of the six cases in which the patients died, right colectomy was performed, in one cecectomy, in two simple excision of the diverticulum, and in one the diverticulum was merely drained.

Choice of Operation.—In ninety-six cases the authors stated their choice of operation.

Fifty-three surgeons performed simple excision or diverticulectomy. Two patients died, a mortality rate of 4 per cent.

One surgeon simply put sulfathiazole in the abdomen and left the diverticulum alone.

Eighteen surgeons performed right colectomy. Two patients died, a mortality rate of 11 per cent.

Three surgeons performed simply closure of the defect.

Fourteen surgeons performed cecectomy, anastomosing the terminal ileum to the ascending colon. One patient died, a mortality rate of 7.1 per cent.

Five surgeons used simple drainage. One patient died, a mortality rate of 20 per cent.

Two surgeons exteriorized the mass in a Mikulicz type of procedure. Neither of the patients died.

Preoperative Diagnosis.—The preoperative diagnosis was stated in sixty-three of the cases. In forty-three it was acute appendicitis, in six appendical abscess, in two perforated appendix, in two ruptured appendix, in two degenerating fibroids, in two salpingitis, in two carcinoma, and in four diverticulitis. Thus, 84 per cent of the stated preoperative diagnoses were of some type of appendicitis. In only 6 per cent of the cases was the condition diagnosed properly before operation as diverticulitis.

Operative Diagnosis.—A major operation was done in a high percentage of the cases: right colectomy in eighteen cases and resection of the cecum in fourteen cases totaling one-third of the entire series. We believe a study of the summary of the findings at operation will explain this. The reason lies in the inability of a surgeon to distinguish between the inflammatory mass of a perforating diverticulum and a perforating carcinoma. Since carcinoma is much more common in the cecum than a diverticulum, a radical approach was adopted. Experience will probably not change this situation, since right colectomy was performed for acute diverticulitis of the cecum by some of the most experienced surgeons reporting in the series.

SUMMARY

Although diverticula of the cecum are considered rather rare, we were able to find records of ninety-nine cases in which operation had been performed because of acute diverticulitis of the cecum. The average age incidence of the patients was less than forty years, making it much lower than for diverticulitis in the remainder of the colon. The cases were about equally distributed between the two sexes, an observation which is also different from most studies on surgical diverticulitis, which show a preponderance of males. More than one-third of the surgeons performed extensive operations such as resection of the cecum or right colectomy. This is understandable in view of the difficulty of distinguishing a perforated and inflamed diverticulum from carcinoma at operation. Eighty-four per cent of the surgeons listing a preoperative diagnosis thought the appendix to be the cause of the patient's symptoms previous to operation.

We believe that acute diverticulitis of the cecum is a surgical disease and will continue to be so for a long time to come, since it seems very difficult to distinguish from appendicitis preoperatively, and since roentgenologic studies of the colon following barium enemas obviously are usually contraindicated when the most probable diagnosis in a case is appendicitis.

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SUBCUTANEOUS HEPARIN IN THE TREATMENT OF ARTERIAL THROMBOTIC DISEASE

Preliminary Report

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THE results in the conservative treatment of venous thromboembolic disease with subcutaneous heparin in the Pitkin menstruum[1-4] have been so gratifying it seemed logical to apply this therapy in the management of arterial thrombotic disease. Exploratory studies were done in fifteen patients in order to observe the clinical deportment of this preparation in the presence of various types of intra-arterial clotting. The clinical observations were so promising that a preliminary report seems justified.

TREATMENT PROGRAM

Heparin/Pitkin menstruum* is a preparation of various amounts of heparin sodium salt, with or without vasoconstrictor drugs, dissolved in the Pitkin menstruum. The dosage of heparin may be varied as indicated in the treatment of the individual patient. In general, the anticoagulant action of heparin sodium salt combined with vasoconstrictor drugs (in the menstruum) is more prolonged than the same amount of heparin sodium salt (in the menstruum) without vasoconstrictor drugs. In thromboembolic venous disease heparin with vasoconstrictor drugs is customarily employed. It is advisable, however, to use heparin without vasoconstrictor drugs in thrombotic arterial disease in order to obviate the complicating factor of arterial spasm. This may necessitate more frequent administration because of the more rapid depletion of the individual deposit.

Body weight and individual reactivity dictate the amount of heparin/Pitkin menstruum to be used in a given case. For the initial injection, body weight is employed as a guide. Patients weighing up to approximately 200 pounds (90.0 kg.) should be given an initial dose of 400 mg. of heparin sodium salt. Subsequently, the dosage should be adjusted according to the intensity of the "heparin effect" as estimated by the coagulation time. Compared with a normal coagulation time of nine to fifteen minutes (Lee-White modification of Howell's method[5]), a coagulation time of thirty to sixty minutes is considered an adequate "heparin effect." In the average case 400 mg. of heparin should be sufficient to keep the patient heparinized for approximately two days.

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Thereafter, 400 mg. should be administered every second day throughout the requisite period of heparinization. If the patient receives a blood transfusion during this treatment period, 400 mg. should be administered immediately following the transfusion, irrespective of when or how many previous deposits have been given. If, for any reason, there is need to stop the effect of the heparinization this can be accomplished immediately by the intravenous administration of 250 to 500 c.c. of whole blood or bank blood not more than three days old.

THE METHOD OF ADMINISTRATION

1. Warm the ampule gently either by holding it under running hot tap water or immersing in a container of hot tap water until the contents become fluid.

2. Draw the contents of the ampule into a dry, sterile 5 or 10 c.c. syringe, using a sterile needle, 18 gauge (two-inch length). After the contents have been drawn up, the 18 gauge needle may be replaced by a 20 gauge needle for the actual injection.

3. Inject the contents immediately into the deep subcutaneous (or superficial intramuscular) tissue, preferably in the anterior or lateral aspect of the thigh. When subsequent injections are required, use the right and left thighs alternately and avoid sites of previous injection. Do not inject into sites where pressure may be exerted upon the injection area.

4. Be certain that the contents of the syringe are not too hot prior to the injection. The syringe and contents should feel only slightly warm.

5. Do not apply either cold or heat to the area of deposition unless for purposes of retarding or accelerating release of the drug.

THE METHOD OF FOLLOWING THE PATIENT'S CLINICAL COURSE

The effect of heparin is judged by and based upon determination of the blood coagulation time which should be estimated daily throughout the period of heparinization. The capillary tube method is inaccurate and should not be used. The Lee-White modification of Howell's method for determination of blood coagulation time is as follows:

1. Place four chemically clean, dry 75 by 10 mm. test tubes in a rack.

2. With a sterile, dry syringe and needle, withdraw a little more than 1.5 c.c. of venous blood from the subject. The test is timed from the moment the blood is first observed in the syringe. Remove the needle from the syringe.

3. Gently distribute a little more than 0.35 c.c. of blood into each test tube. Discard the last air-containing fraction.

4. All glassware, syringes, and needles must be absolutely dry. Moisture, alcohol, etc., invalidate the determination.

5. The vein must be negotiated cleanly. If difficulty is encountered, it is best to use a fresh needle and syringe. Even a small amount of tissue juice aspirated into the syringe will give a false result.

6. Once the blood is placed in the test tubes, they must be disturbed as little as possible while observing for the end point. It will be noticed that well-heparinized blood will sediment very rapidly. The tubes should not be shaken after sedimentation of the blood. Look for clotting in the red cell layer as well as in the plasma layer, by gently tilting the tubes. In unclotted blood the red cell layer will flow as the tube is angled.

7. First, gently tilt one tube and note the flow of the red cell layer. If the flow is rapid, discard the tube and wait about five minutes before the second tube is angled. In this way the end point may be approximated, and then finally accurately determined from the third or fourth tubes. Once any of the tubes is disturbed, it should be discarded.

8. The patient's coagulation time should be determined before heparinization for control purposes. After that the coagulation time should be estimated daily (twenty-four hours after the heparin injection and immediately before the next heparin injection).

Papaverine is used concomitantly in liberal dosages, first by the intramuscular or intravenous route in 1 to 3 gr. dosages, and subsequently by mouth in maintenance dosages of 1 to 1½ gr. every four hours. Paravertebral sympathetic blocks are used when indicated and repeated whenever necessary in the presence of protracted vasospasm. The vasospasm is apparent for the most part during the early stages of the treatment program before heparinization is in full effect. Rarely is sympathetic block necessary following the first or second deposit of heparin/Pitkin menstruum. Additional treatment measures include antibiotics parenterally and topically to combat infection, symptomatic therapy, adequate sedation, and control of diabetes when present.

TECHNIQUES OF FOLLOWING AND EVALUATING THE PROGRESS OF THE PATIENT

Thermocouple, oscillometric, and histamine skin tests were performed routinely on all of the patients before heparinization was initiated. These studies were carried out repeatedly, thereafter, in order to assess the response to the treatment program.

The clinical criteria of improvement were: (1) the restoration to the compromised tissues of normal color, tone, and lividity; (2) delineation of any gangrenous process; (3) decrease in pain; (4) increase in pulsations of blood vessels of the affected limb. The clinical improvement was usually reflected in the oscillometric studies, surface temperature readings, and histamine skin reactions.

CLINICAL MATERIAL

The effectiveness of heparin in the Pitkin menstruum was investigated in this series of cases merely as an exploratory study. The patients represented many aspects of arterial thrombotic disease and served adequately as a means of appraising the clinical response to this preparation. The various arterial lesions included in this series of 15 patients (Table I) were intra-arterial emboli (5 cases), diabetic gangrene (6 cases), thromboangiitis obliterans (3 cases), and ergotism (1 case).

DISCUSSION OF RESULTS

Although the pathogenesis differs in the various diseases enumerated in Table I, the common denominator is thrombus formation. While recanalization of thrombus may supervene sufficiently to maintain the vascular stream and retain the viability of the affected limb, as a rule death of tissue and gangrene is the ultimate fate in the untreated case of intra-arterial thrombotic occlusion. Through the use of anticoagulants, such as heparin, propagation of thrombus is inhibited, the patency of the affected vessel and uninvolved collaterals is maintained. As a result, loss of tissue is minimized or completely obviated and recanalization of the affected major vessel is enhanced.

Of the five patients with intra-arterial embolization the result was successful in four and there was one treatment failure. A favorable outcome in all of the four patients was indicated by disappearance of cyanosis, prompt amelioration of pain indicating restoration of circulation and, more important, the absence of necrosis. The clinical improvement was documented by elevation

TABLE I. HEPARIN/PITKIN MENSTRUUM IN THE TREATMENT OF FIFTEEN PATIENTS WITH ARTERIAL THROMBOTIC DISEASE

CASE NO.	SEX	AGE	DIAGNOSIS	DURATION	CLINICAL FINDINGS PRIOR TO THERAPY	HAPARIN TREATMENT DAYS	HAPARIN TREATMENT AMT. (MG.)	RESULTS AND REMARKS
1. D. P.	M	50	Embolus left femoral artery, arteriosclerotic heart disease, auricular fibrillation	13 hr.	Absent left femoral artery pulsation, cyanosis to knee, extremity cold with loss of tissue tone; oscillometric readings at knee and ankle, 0; skin temperature, first toe, 74.5° F.; histamine test, doubtful reaction	12	2,100	Femoral pulsations restored; oscillometric* readings at knee, 0.5; ankle, flicker; skin temperature, first toe, 78.5° F.; histamine skin test, foot, normal
2. S. E.	F	60	1. Embolus right femoral artery, arteriosclerotic heart disease 2. Embolus right brachial artery	8 hr.	1. Right foot cold, markedly pallid; oscillometric readings at thigh, knee, and ankle, 0; skin temperature, first toe, 78° F.; histamine test, absent	5	1,050	Color normal; oscillometric readings at knee and thigh, flicker; skin temperature and histamine skin test perceptibly improved
					2. Right arm cold and pallid; oscillometric readings at wrist and elbow, 0	9	1,350	Color normal; no necrosis
3. R. J.	M	49	Embolus right popliteal artery	20 hr.	Dorsalis pedis and posterior tibials absent, leg cold and cyanotic to knee, painful and tender	9	1,350	Dorsalis pedis and posterior tibial pulsations present; color and tissue tone normal, pain disappeared; skin temperature normal
4. H. P.	M	70	Embolus right popliteal artery, coronary artery thrombosis	3 wk.	Dorsalis pedis, posterior, tibial, and femoral pulsations, absent, right leg cyanotic lower two-thirds with loss of tissue tone, skin cold, pain severe; oscillometric readings at thigh level, 0	5	900	Gangrenous process arrested, amputation performed because of intractable pain
5. R. W.	M	38	Saddle embolus of aorta, rheumatic heart disease, auricular fibrillation	14 hr.	Right femoral palpable, all other vessel pulsations both extremities absent, pain, pallor, coldness of both feet; no response from sympathetic block; oscillometric readings at knees and ankles, 0	23	3,800	Normal color restored; oscillometric readings right knee, 0.5; right ankle, 0; left knee, 0.5; left ankle, 0
6. S. K.	F	72	Diabetic gangrene	3 days	Gangrene of left second toe with marked swelling extending to foot	14	2,450	Gangrenous process controlled until patient refused further treatment; toe finally amputated
7. L. S.	F	52	Diabetic gangrene	4 mo.	Gangrene and mummification of first, second, and third left toes; oscillometric readings at knee and ankle, 0; histamine skin test, left foot, 0	7	1,100	Gangrene extended requiring amputation
8. A. B.	F	60	Diabetic gangrene	2 wk.	Patchy cyanosis and early gangrene of left foot and heel, gangrene of left fourth toe which finally extended to other toes; oscillometric readings left knee, 0.5, left ankle, 0; skin temperature, first toe, 81° F.; dorsum, 80° F.; histamine skin test, foot, 0	17	2,850	Gangrene finally controlled and demarcated, patchy cyanosis disappeared, toes sloughing off; oscillometric readings, thigh, 1.0; ankle, 0.5; skin temperature, first toe, 91° F.; dorsum, 89° F.; histamine skin test, foot, normal
9. M. R.	F	59	Diabetic gangrene	2 mo.	Gangrene of left big toe with cellu-	19	2,150	Cellulitis disappeared, gangrene

9.	M. R.	F	59	Diabetic gangrene	2 mo. dry 2 days wet	Gangrene of left big toe with cellulitis of foot and adjoining two toes despite penicillin, dorsalis pedis and posterior tibial absent; oscillometric readings thigh, 0.5; knee, flicker; ankle, flicker	19	2,150	Cellulitis disappeared, gangrene delineated with sloughing off of toe; oscillometric readings, thigh, 1.0; knee, 0.5; ankle, flicker
10.	M. K.	M	66	Diabetic gangrene	4 wk.	Gangrene left third toe and adjoining 1½ inches of foot, cellulitis with bullae of second toe and adjoining half of foot which spread despite sulfonamides and penicillin; pallor of foot on elevation	13	2,500	Gangrene demarcated, cellulitis subsided, toe sloughing off
11.	M. N.	F	73	Diabetic gangrene	3 wk.	Extensive gangrene of medial surface of left big toe and entire third and fifth toes and adjoining part of foot, necrotic blister on heel, complicating infection with fetid odor; penicillin alone ineffectual; oscillometric readings knee, 1; ankle, flicker; amputation indicated but patient refused to consent	26	2,650	Gangrene delineated with sloughing off of third toe, infection controlled with residual open wound on plantar surface, skin around ulcer healthy; oscillometric readings, knee, 2.0; ankle, 0.75
12.	S. K.	M	38	Thromboangiitis obliterans	90 days	Extensive gangrene of right ankle and foot with severe secondary infection; oscillometric readings, knee, flicker; ankle, 0	12	2,150	Conjoint heparin and penicillin treatment interrupted because of lack of cooperation of patient; gangrene extended resulting in amputation
13.	J. C.	M	42	Thromboangiitis obliterans	30 days	Left radial pulse absent; left hand, especially dorsum, painful, blanched with cyanosis at periphery; hand cold with loss of tissue tone	20	2,050	Left radial pulse restored with disappearance of blanching, surrounding cyanosis, coldness and pain; improvement so singular patient enabled to return to work as bartender
14.	C. C.	M	42	Thromboangiitis obliterans, thrombophlebitis migrans	5 wk.	Extensive thrombophlebitis of left leg with swelling, pain, and positive Homans' sign, diminished arterial pulsations with history of intermittent claudication; reduced to absent oscillometric readings of left lower extremity	14	2,400	Rapid resolution of thrombophlebitis with disappearance of pain, swelling and tenderness; increase in arterial pulsations
15.	B. G.	F	60	Ergotism	18 hr.	Bilateral, intense, cold cyanosis of hands with absent radials; no response to sympathetic block; oscillometric readings at wrists absent; skin temperature, right thumb, 82.5° F.; left thumb, 78° F.	3	750	Both radial pulsations present and normal, color healthy; oscillometric readings both wrists, 1.0; skin temperature, right thumb, 85° F.; left thumb, 88° F.

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*The Boulitte oscillometer was used. Normal readings are: wrists, 1 to 3; thighs, 4 to 8; knees, 4 to 8; ankles, 2 to 3.

of surface temperature, increased oscillometric readings, and intensification of the histamine skin reaction. It is noteworthy that heparin/Pitkin menstruum therapy was initiated in the four successfully treated patients within eight to twenty hours after onset. The one failure (Case 4) was admitted for treatment three weeks after the embolic arterial occlusion. Failure to respond was therefore not unexpected in view of the fact that one to two days after embolic occlusion the functional pathology no longer consists merely of stagnation of blood with some complicating perivascular extravasation. Thereafter the stagnant blood becomes fibrinous and undergoes progressive organization with irreversible tissue changes. It is at this stage that anticoagulant therapy is futile. Fortuitously embolic occlusion is usually accompanied by marked vasospasm; the resultant pain is so severe, and excruciating and difficult to endure, that patients enlist medical aid at an early stage when the treatment program might be expected to be more effective.

Of the six patients with diabetic gangrene, five had a favorable result and one suffered an amputation. In this type of patient the results understandably are not as dramatic as in the embolic group because the thrombosis develops insidiously, progresses at a slower tempo, and is usually unaccompanied by severe pain of the type that demands prompt relief. These patients, therefore, are observed at a later stage when some necrosis and gangrene have actually developed. If untreated the thrombosis is progressive and more tissue is inevitably involved with resultant loss of limb. Thus, with diabetic gangrene the chief objective is to prevent further intravascular clotting, thereby salvaging as much tissue and limb as possible.

In the five patients with satisfactory outcome, heparin/Pitkin therapy was instituted from three to sixty days after the onset of the gangrene. Significantly, in these five patients where only mottling cyanosis was present indicating an early stage of thrombosis, these affected areas improved in color under treatment and the skin temperatures rose to a higher level. Those areas already the seat of dry gangrene obviously had to be sacrificed. It is interesting to note that one patient (Case 10) was given extensive treatment for four weeks at home with both penicillin and sulfonamides despite which the lesion progressed and necrosis occurred. Following admission to the hospital penicillin was continued but it was not until after two subcutaneous deposits of heparin in the Pitkin menstruum that the necrotic lesion showed a definite area of demarcation following which the erythema and cellulitis-like lesion receded and the bullae cleared up. Finally, the erythema and bullae were no longer evident and the gangrenous area was delimited to the third toe and part of the plantar surface of the foot. In the one treatment failure (Case 7) the first, second, and third toes were mummified when therapy was begun about four months after the initial appearance of gangrene.

Of the three patients with thromboangiitis obliterans, two responded successfully with restoration of patency of the affected vascular channels, resumption of circulation in the affected limb, and amelioration of pain and claudication. The disappearance of blanching in the ulnar distribution during the

therapy (Case 13) was so striking that it was difficult to distinguish between the affected and contralateral limb. The one treatment failure (Case 12) eventuated in amputation. This patient had involvement of the toes and foot up to the ankles, which started three months prior to admission. He was very toxic and had a high swinging temperature. Because of lack of cooperation the conjoint program of heparin and penicillin was suspended following which the gangrene rapidly spread and extended. Amputation was ultimately carried out in another institution.

One patient had early gangrene of both hands due to ergotamine tartrate which was administered for pruritus due to jaundice. After several injections of the drug the patient developed severe cyanosis and coldness of both hands. On examination both radial pulses were absent, the skin temperature was subnormal, and the histamine skin test was negative. Both stellate ganglia were blocked without appreciable results. Subcutaneous heparin/Pitkin menstruum was started about eighteen hours after onset and prompt improvement was manifest after two deposits. Two weeks later the radial pulses were palpable and of good volume, normal color was restored, and the skin temperature, oscillometric readings, and histamine skin tests were all within normal limits.

SUMMARY AND CONCLUSIONS

Heparin/Pitkin menstruum has proved to be an effective agent in the treatment of arterial thrombotic lesions. Clinical observations in fifteen cases of intra-arterial thromboses have shown satisfactory response in terms of amelioration of pain, restoration of normal color, tone, and lividity to the tissues, delineation of any gangrenous process, and increase in pulsation of blood vessels in the affected parts. While this series of patients is too small to lend itself to any statistical review the results are sufficiently encouraging to justify further expansion of this exploratory project. In general, those patients fared best who received the optimum treatment program within a few hours after the occlusive process became evident.

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THIOURACIL AND CARCINOMA OF THE THYROID

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THE marked proliferation produced in the thyroid by thiouracil has aroused in the minds of many the question of possible subsequent development of malignancies in the patients so treated. This marked proliferation along with the high incidence of carcinoma in toxic nodular goiter has led Hinton and Lord[1] to state that thiouracil is contraindicated in the treatment of toxic nodular goiter. Pertinent also is the experimental work of Bielschowsky[2] who noted that rats fed thiourea and 2-acetaminofluorene developed adenomatous or anaplastic invasive tumors of the thyroid while either drug given alone did not produce such changes.

We have recently encountered a carcinoma in a patient with diffuse toxic hyperplasia of the thyroid who was treated preoperatively with thiouracil and iodine. Because of the possible carcinogenic activity of thiourea this case is reported here.

CASE REPORT

History.—Mrs. W. H. D., a 56-year-old white woman, was first seen on Aug. 31, 1945, complaining of nervousness, anorexia, and a loss of forty-nine pounds in weight during the previous year. She had also noted increasing bulging of the eyes with impairment of vision. She had noted no increase in cold tolerance or heat intolerance. There were no gastrointestinal symptoms. The past history was entirely negative.

Physical Examination.—Temperature was 98.6° F., pulse 108 to 120, respirations were 20, blood pressure 158/90. Body weight was 115 pounds. The general appearance of the patient was that of an emaciated, nervous white woman with marked exophthalmos and appearing to be about the stated age. The ears, nose, and mouth were negative. The eyes showed marked exophthalmos with poor vision partially corrected by glasses. The neck showed a slight smooth fullness in the region of the thyroid; there was no bruit. The lungs were clear. The heart rhythm was regular but rapid and the sounds were of good quality. There were no murmurs. The pulse was forceful with a pulse rate varying, at different times, from 108 to 120. The abdomen and extremities were negative. The only positive finding on neuromuscular examination was a constant fine tremor of both hands which was exaggerated on extension of the arms and separation of the fingers.

Laboratory.—Basal metabolic rate was + 36, hemoglobin 13.6 Gm., red blood cells 4,100,000, white blood cells 7,200, with a normal differential count. The urine was negative.

Treatment and Progress (see Table I).—Treatment was begun on Aug. 31, 1945, with 0.2 Gm. of thiouracil each day for one week. On September 7 the basal metabolic rate was + 21, the pulse 98, and the white blood cells 9,000 with 64 per cent neutrocytes. Thiouracil was then increased to 0.3 Gm. daily for one week. On September 14 the basal metabolic rate was + 20, the pulse 92, and the white blood cells 7,900 with 60 per cent neutrocytes. At this time the weight was 116½ pounds. Thiouracil was then increased to 0.4 Gm. daily and continued for six days. On September 20 the basal metabolic rate was + 17, body weight 120 pounds, pulse 88, and the white blood cells 7,100 with 62 per cent neutrocytes.

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TABLE I. PREOPERATIVE THERAPY

DATE	DRUG THERAPY DAILY DOSE THIOURACIL (GM.)	LUGOL'S (GTT.)	TOTAL THIOURACIL (GM.)	B.M.R.	BODY WEIGHT	PULSE	W.B.C.
8/31/45				+36	115	108-120	7,200
8/31 to 9/7	0.2		1.4	+21		98	9,000
9/7 to 9/14	0.3		2.1	+20	116½	92	7,900
9/14 to 9/20	0.4		2.4	+17	120	88	7,100
9/20 to 9/27	0.4		2.8	+ 9	121	72	8,100
9/27 to 10/4	0.2	20	1.4	+ 2	126¾	72	7,800
10/4 to 10/10	None	20	0.0				
			10.1				

Thiouracil was continued at 0.4 Gm. daily until September 27 when the basal metabolic rate was + 9, body weight 121 pounds, pulse 72, and the white blood cells 8,100 with 58 per cent neutrocytes. On this date thiouracil was reduced to 0.2 Gm. daily and in addition 10 Gtt. of Lugol's solution was given twice daily. On October 4 the basal metabolic rate was + 2, body weight 126¾ pounds, and the pulse 72. The white blood cell was 7,800 and the neutrocytes 60 per cent. Thiouracil was discontinued but the Lugol's solution was continued in doses of 10 Gtt. twice daily up to the time of operation on October 10.

On October 10 a partial resection of both lobes of the thyroid was done. Postoperative recovery was uneventful. Because of the pathologic findings she was treated with x-ray to the thyroid region receiving 3,500 r. through two portals between October 19 and November 8 at a rate of 200 r. each day. Each portal measuring 8 by 8 cm. was treated on alternate days. To date, five months after surgery, there has been no clinical evidence of recurrent tumor and the patient is symptom-free.

Pathology.—

Gross (S45-2140): The specimen consisted of two pieces of thyroid tissue having a combined weight of 17.5 Gm. Externally they were pale brown, normally lobulated, and partially covered by a transparent capsule. On section they were firm, normally lobulated, and pale brown. In the central portion of the lower pole of each lobe there was an irregular white zone of fibrous scarring measuring about 0.7 cm. in diameter. One of these showed a few small irregular flecks of calcification.

Microscopic: Multiple sections taken through various portions showed an unusually varied picture. The majority of the acini were small and contained scant colloid. This was notched at the margins. The acini were lined by large cuboidal to columnar cells which had a faintly eosinophilic and partially vacuolated cytoplasm. The nuclei were small and vesicular. In addition there were several small nodules which were composed of acini which contained a granular basophilic material and which were lined by flattened faintly eosinophilic cells. Some of these cells, however, showed a transition to large eosinophilic cells resembling Hürthle cells. The stroma through most of these portions was scant, fibrous, and showed scattered foci of lymphocytic infiltration.

Multiple sections taken through the white zones noted in each lobe grossly showed in both of them a dense fibrous tissue. Within this fibrous tissue there were well-formed gland spaces lined by amphophilic cells which varied from a cuboidal to a columnar in shape (Fig. 1). These cells were more hyperchromatic than thyroid cells elsewhere. There was a marked papillary pattern to their arrangement at some points. In addition, the nuclei here were irregular in size, large, and showed prominent nucleoli. There were several small arteries and about these were small glands lined by atypical cells similar to the main cells in this portion and suggesting an invasion of perivascular lymphatics. There were irregular strands of glands lined by these atypical cells extending irregularly through both nodules (Figs. 2 and 3).

The picture in the second portion was entirely different from that seen elsewhere in the gland. Here the gland spaces were atypical and there was great variation in the nuclei

which indicated that these lesions must be regarded as malignant. Blood vessel invasion was not noted but the cells were sufficiently atypical to warrant a diagnosis of malignancy. It is interesting that the change occurred in both glands which along with the papillary pattern suggested the possibility of the lesion having developed from previously existent papillary cystadenomas.

The picture throughout the remainder of the gland showed the marked hyperplasia encountered with thiouracil therapy and in addition the changes seen with preoperative iodine therapy.

Diagnosis: The diagnosis was diffuse toxic hyperplasia of the thyroid and papillary adenocarcinoma of the thyroid.

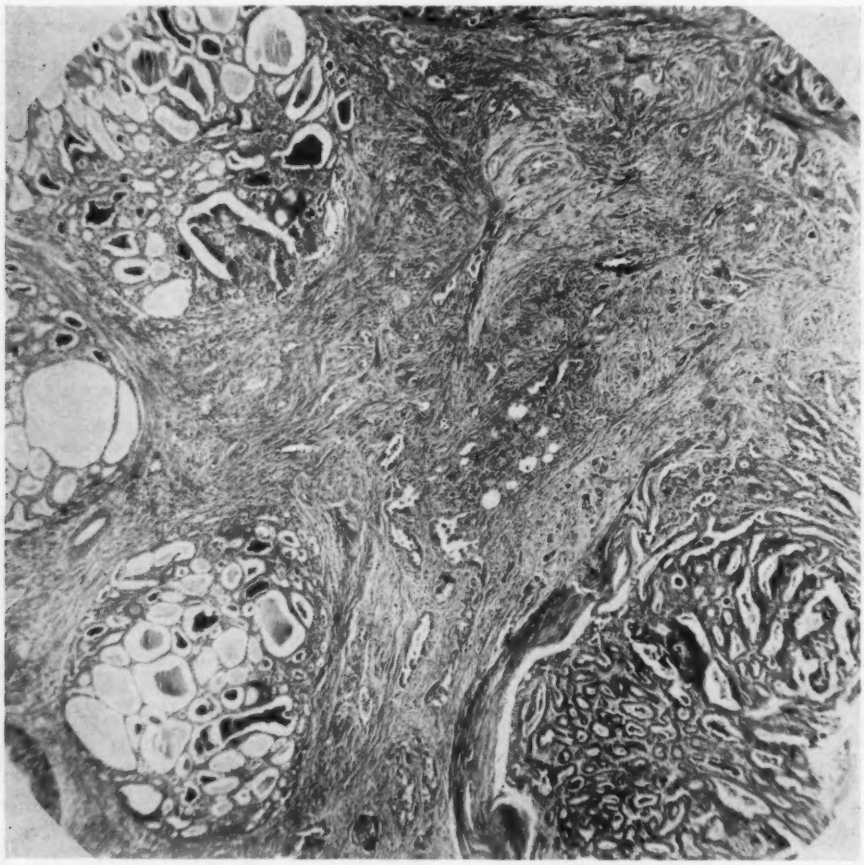

Fig. 1.—Low-power view of a tumor zone. Note the marked difference between the more normal thyroid groups on the left and the tumor through the center of the field and in the right lower corner.

DISCUSSION

The zones of tumor in this gland have all the characteristics of a malignant growth with considerable variation in cell and nuclear size and large nucleoli. The lesions were small and represent an incidental finding for the clinical symptoms and the pathologic findings were primarily those of hyperthyroidism and not neoplasm.

The question then arises as to the possible relation of the neoplastic lesion to the preoperative thiouracil therapy. The similarity between a thiouracil-

treated gland and the gland of hyperthyroidism before iodine therapy has been pointed out by Graham,[3] Shirer and Cohen,[4] and others. Broders and Parkhill[5] also noted this hyperplasia and in addition reported the occurrence of mitoses in the epithelial cells of the acini. These findings serve to raise the question as to how far the growth stimulation produced by thiouracil will progress.

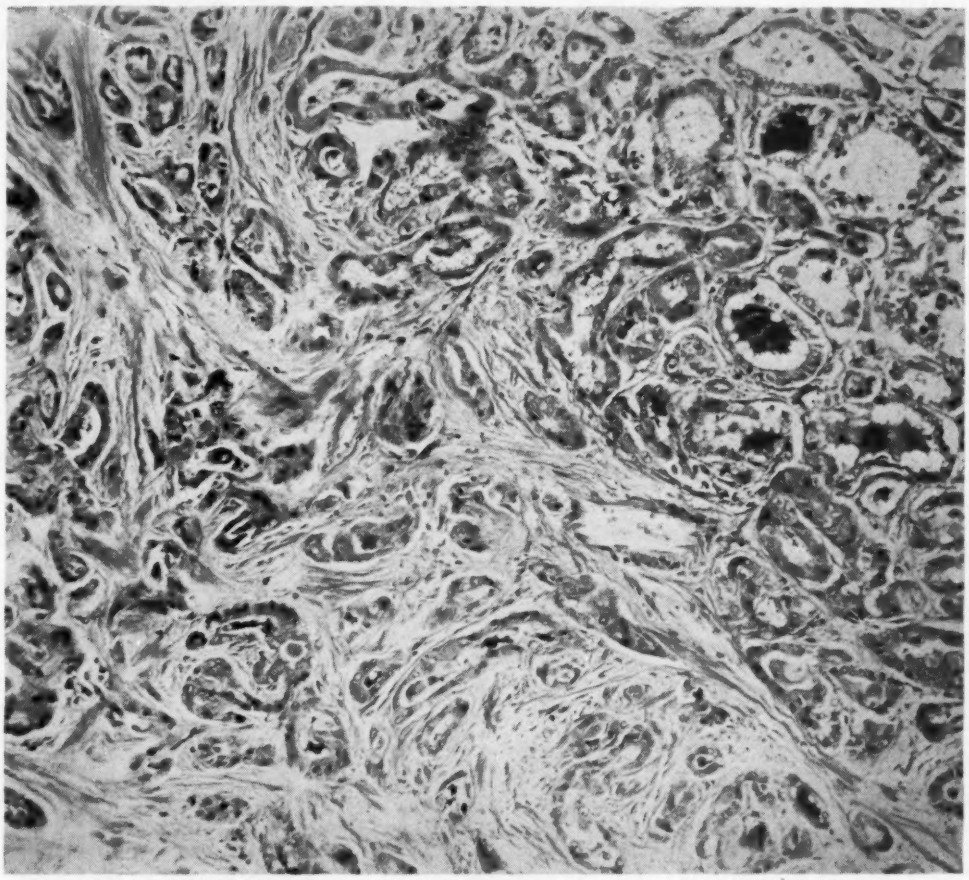

Fig. 2.—Showing atypical distorted glands extending throughout the tumor region. (Phloxine-methylene blue ×250.)

On the experimental side, of particular interest, is the work of Bielschowsky,[2] who noted that a combination of thiourea and 2-acetaminofluorene produced malignant tumors of the thyroid in rats. Wilson, DeEds, and Cox[6] first noted the carcinogenic activity of 2-acetaminofluorene and reported neoplasms occurring in many organs in rats fed this drug. Bielschowsky[7] reported that, when administered orally, 2-acetaminofluorene produced carcinomas of the lungs, salivary glands, liver, pancreas, and breast, and leucemias and lymphosarcomas. None of these animals developed carcinoma of the thyroid. Bielschowsky then fed rats thiourea and again no tumors of the thyroid developed, but when rats were fed thiourea and 2-acetaminofluorene, anaplastic epithelial tumors of the thyroid developed. It thus becomes apparent that thiourea is capable of focusing the activity of at least one carcinogenic agent upon the thyroid.

Of further pertinent interest in the role of thiouracil in the development of carcinoma in this case is the rarity of carcinoma in diffuse toxic hyperplasia of the thyroid. Ward[8] encountered only one case of carcinoma in 1,900 instances of diffuse toxic goiter, which agrees with the statistics cited by Boyd[9] to the effect that Wegelin encountered only 13 malignancies of the thyroid in 13,426 autopsies in Berlin, where the incidence of goiter is low. We, therefore, feel that the occurrence of the carcinoma in this case is unusual and that

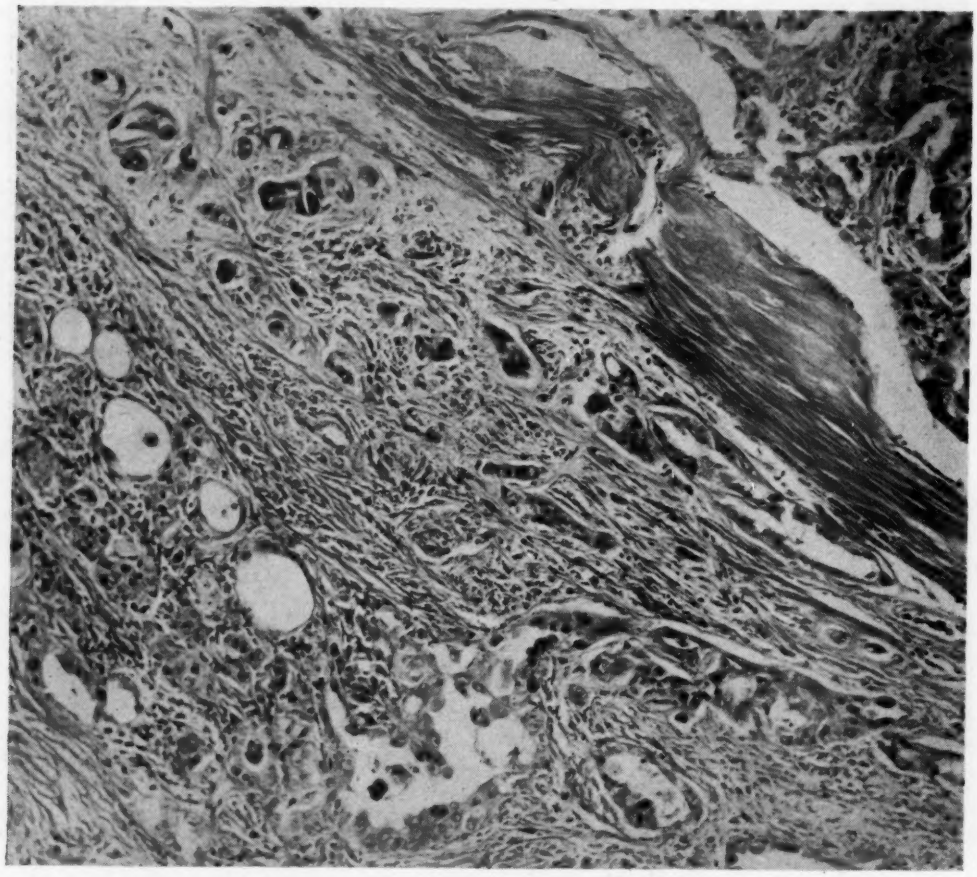

Fig. 3.—Another portion of tumor tissue showing disorderly growth. Note the variations in cellular and nuclear structure. (Phloxine-methylene blue ×250.)

in consideration of previous statistical studies the thiouracil may have played a part in the development of the growth. The fact that the gland showed a diffuse hyperplasia makes the occurrence of a carcinoma more unusual than if the gland had shown a nodular type of goiter. In nodular goiter the incidence of carcinoma is high, occurring 4.8 per cent in the series reported by Ward[8] and 7.2 per cent in that reported by Cole, Slaughter and Rossiter.[10] Hinton and Lord[1] pointed out that in this last series of 193 cases of nontoxic nodular goiter 17.1 per cent showed carcinoma and that in the group of nontoxic solitary nodules the incidence was 24 per cent. These statistics led them to the conclusion that all nontoxic goiters should be removed surgically because of the high

incidence of carcinoma and that because of its carcinogenic potentialities thiouracil is contraindicated in the treatment of nodular goiter. Our case would lend support to this last hypothesis.

We cannot, of course, definitely state that the carcinoma developed in this individual because of the thiouracil therapy. There is one previous mention of carcinoma in a patient treated with thiouracil, this instance simply being listed by Moore and associates[11] in a table of cases treated preoperatively with the drug. There is no discussion of the case in their text. Future reports of similar cases will be necessary for any evaluation of the role of thiouracil in the development of carcinoma of the thyroid in man.

SUMMARY

A case of early carcinoma of the thyroid is reported occurring in a diffuse toxic hyperplasia of the thyroid which was treated preoperatively with thiouracil and iodine.

The question of the carcinogenic potentialities of thiouracil is raised, but this will be determined by subsequent reports of similar cases.

We are indebted to Dr. A. P. Stout and Dr. V. K. Frantz of the College of Physicians and Surgeons, Columbia University, New York, N. Y., for reviewing this material and having the photomicrographs prepared.

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MISCONCEPTION OF THE GUBERNACULUM TESTIS

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JOHN HUNTER (1786), who discovered the gubernaculum testis, described it in part as "a substance which runs down from the lower end of the testis to the scrotum." A century later, Lockwood (1887, 1888) contributed to confusion when he reported that the lower end of it fans out to produce six strands of attachment: (1) "to Scarpa's triangle," (2) to the pubis, (3) to the root of the penis, (4) to the scrotum, (5) to the perineum near the tuberosity of the ischium, and (6) to the sphincter ani.

Actually, in a fetus of the seventh lunar month, the upper end of the gubernaculum is attached to the tail of the epididymis (Wells, 1943). The lower end of it does not reach the scrotum but terminates at the bottom of the inguinal bursa of Klaatsch (1890).* This bursa is the sac that receives the testis and that originates by eversion of four layers of the abdominal wall (peritoneal, transverse, internal oblique, and external oblique). The bursa may be shelled out of the scrotum without tearing more than areolar tissue, as it may be also in the newborn (R. H. Hunter, 1926). Similarly, in the cadaver of an adult man, the spermatic sac† and the scrotal sac may be readily separated by blunt dissection‡ (see insert, Fig. 1).

However, it is a common notion that in patients subjected to surgery for undescended testis it is possible to identify the gubernaculum as a definite "ligament" which extends from testis to scrotum or from testis to some non-scrotal structure (Eisendrath, 1926; Thompson, Bevan, Heckel, McCarthy and Thompson, 1937; Abrahamson, 1942; Bishop, 1945; Schutt, 1945; Ormand, Cothran, and Singister, 1945).

The main object of the present study was to determine whether the gubernaculum could be identified in such patients. A second and related objective was to search for any discrete band of tissue which might account for the widespread opinion that the gubernaculum extends below that part of the inguinal bursa which normally becomes the spermatic sac.

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*As already pointed out (Wells, 1943), the extent of the gubernaculum in embryos younger than the 43 mm. stage deserves additional study.

†This term was coined by E. A. Boyden to designate that part of the bursa which contains the testis. It is quite useful: (1) as a companion term to "spermatic cord" and (2) as a means of emphasizing the fact that as outpocketings of the abdominal wall the spermatic sacs are to be considered in a different category (both anatomically and embryologically) from the scrotal sacs which are outpocketings of the skin and tela subcutanea.

‡In the female, the homologue of the gubernaculum is the ligamentum teres uteri. The primordium of these structures, appearing before it is possible to determine the sex of the embryo, should be called the "genito-inguinal ligament," a term introduced by Waldeyer (1889). Presumably the round ligament terminates inferiorly at the fundus of the inguinal bursa; the bursa develops in both sexes. Anson and Ashley (1941) stated that the round ligament "is inserted by diverging fibers into the superficial fascia of the labium majus." In any event, after disappearance of the canal of Nuck, the three persisting layers of the bursa are the ones that surround the lower portion of the round ligament.

In regard to methods, four patients were selected for careful study. During surgery, the procedure was: (1) to identify the inguinal bursa, (2) to search for a cord of tissue below its blind end, (3) to open the bursa in order to note any manifestations of a gubernaculum on its posterior aspect, (4) to tag crucial portions of the bursa for the purpose of orientation in microscopic studies, and (5) to remove the bursa plus attached strands of tissue (after

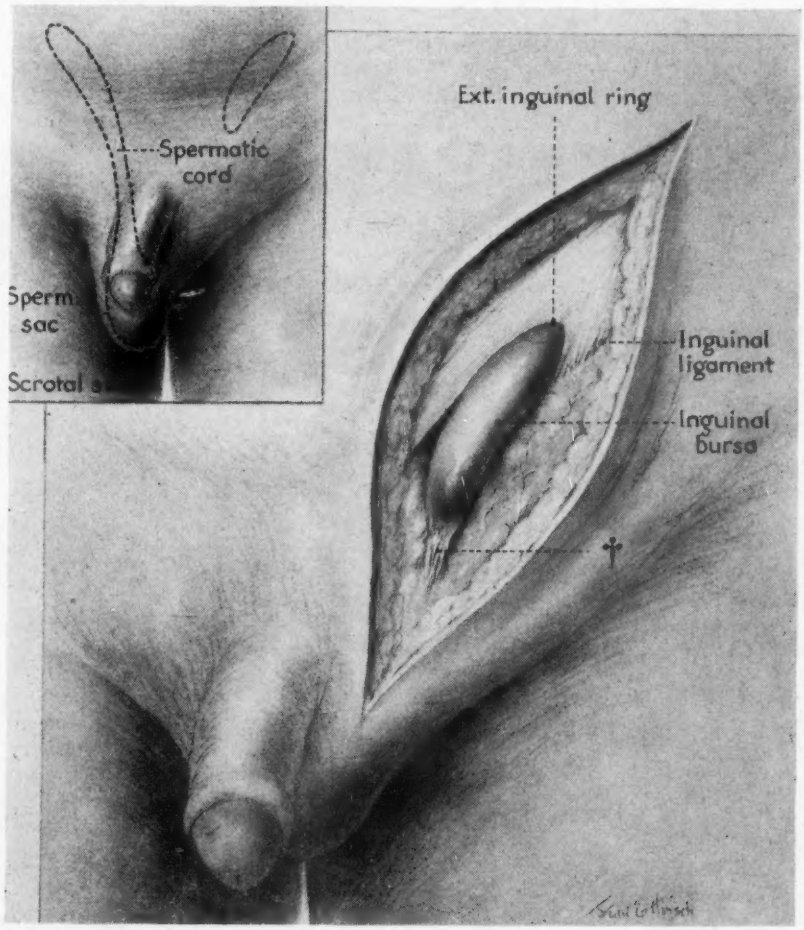

Fig. 1.—The left inguinal bursa as it appeared after areolar tissue had been removed from its anterior aspect. The dagger marks a "ligament" of connective tissue that was produced by blunt dissection (such "ligaments" are commonly mistaken for the gubernaculum testis). The insert shows that if the right testis had reached the scrotum the bursa would have become the spermatic cord and the spermatic sac.

freeing the testis). The surgical specimen thus obtained was fixed by placing it in formol-Zenker solution. Portions of the specimen were passed through paraffin and sectioned at 6μ. Certain sections of each portion were stained, three methods being used (Mallory's triple, Dominici's, and hematoxylin and eosin).

In anticipation of that which follows, it was found that sections of a gubernaculum could not be identified in any of the microscopic preparations

of the four surgical specimens. Therefore, it was decided to present only one case, namely, the one which turned out to be the most instructive. A clinical and surgical history of the patient is presented here.

CASE REPORT

D. B. (U.H. No. 768109), white male aged 12 years, was first seen at the University Hospitals on June 24, 1946. The main complaint was failure of descent of the testis, bilaterally. In the summer of 1945 he had received a series of sixteen injections of gonadotrophic hormone (''gonadotropin,'' dose unknown) by his local physician without benefit. While receiving the injections, a mass was noted in the left inguinal region, which caused the patient no discomfort but which persisted.

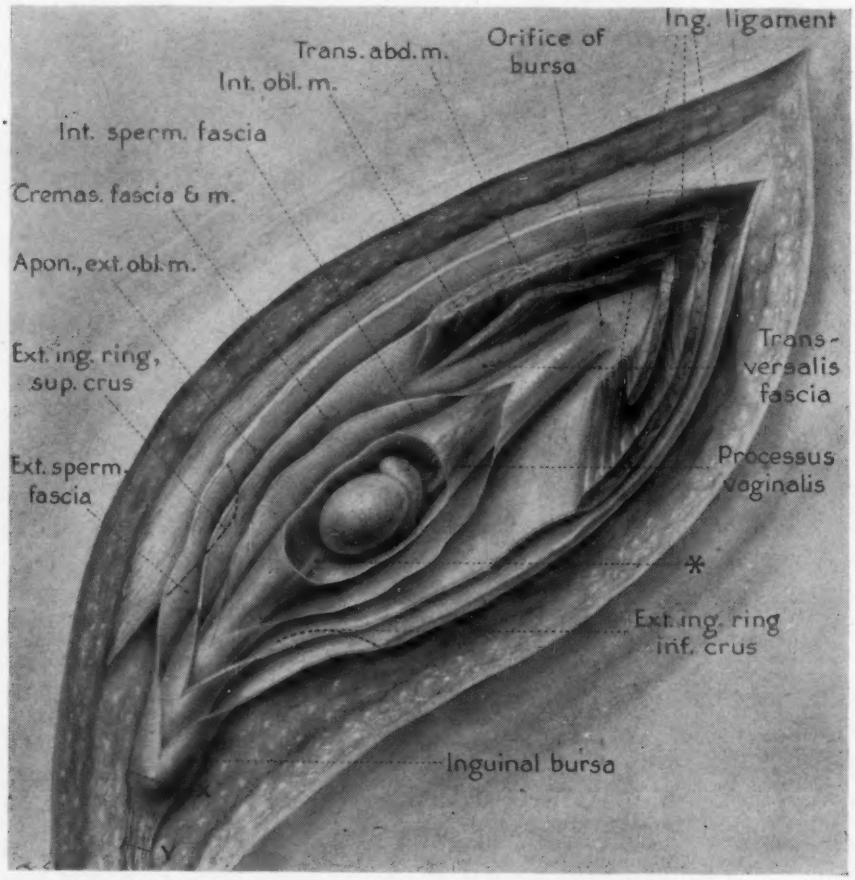

Fig. 2.—The left testis as it appeared after the bursa had been opened. The asterisk marks the site where a gubernaculum, if present, should be expected. The dotted lines (*x* and *y*) indicate a block of tissue that was sectioned serially and vertically (see text).

The family history was of interest in that the patient's father and two brothers each had unilateral failure of descent of the testis.

Physical examination on admission revealed a well-nourished and well-developed 12-year-old white boy who did not appear ill or in distress. The examination apart from bilateral cryptorchidism and an easily reducible left inguinal hernia was essentially negative. It was thought that the left testis could be felt high in the inguinal canal but the right testis could not be palpated at all.

On July 1, 1946, a left inguinal hernioplasty and orchiopexy were done under cyclopropane anesthesia. The hernioplasty was done according to the method of Ferguson (1899) and the orchiopexy as described by Wangensteen (1935).

Turning to observations in this case, the inguinal ring was visible as soon as the skin and tela subcutanea had been incised. A structure in the inguinal canal, subsequently identified as the testis, could be moved upward and downward by exerting manual pressure, but it would not pass through the external ring. The first indication of an inguinal bursa to appear was an indistinct outline of its fundus. Below the fundus, it was impossible to see or to palpate any cord of tissue that might be said to resemble a gubernaculum. Fig. 1 illustrates the bursa as it appeared after strands of connective tissue had been stripped from its anterior wall and after a "ligament" of connective tissue had been "created" by blunt dissection (marked by dagger).

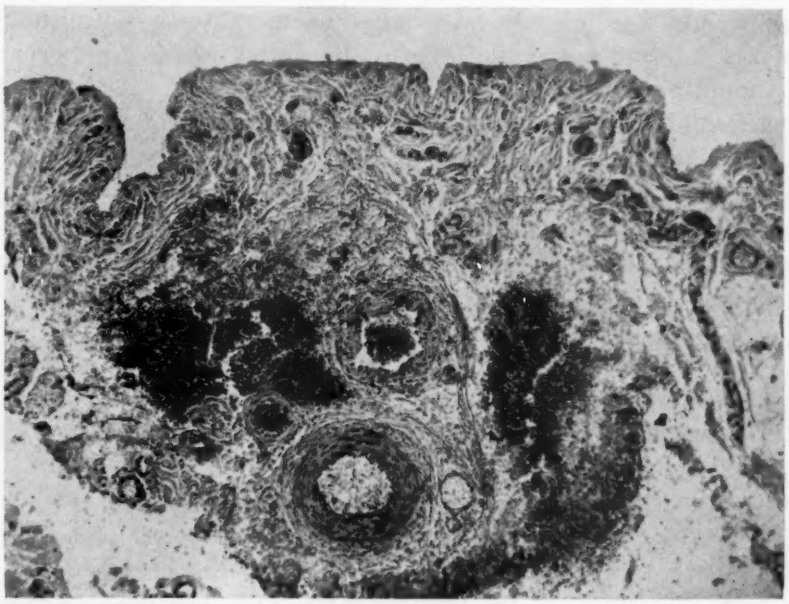

Fig. 3.—Photomicrograph of a transverse section of the two inner layers of the bursa at the site where a gubernaculum, if present, should be expected. The section passes through a longitudinal ridge of peritoneum (asterisk in Fig. 2 and top of photomicrograph). The photograph shows that this ridge was caused by blood vessels in the internal spermatic layer. There are two large areas of hemorrhage. (Dominici's stain, ×90.)

When the bursa was opened, the testis could be seen through its thin covering of peritoneum (Fig. 2). A gloved finger in the peritoneal sac (lining of bursa) could enter the abdominal cavity by passing through the patent orifice of the bursa.* Extending down from the tail of the epididymis was some unknown, retroperitoneal structure that elevated the peritoneum to produce a longitudinal ridge (asterisk). Aside from its narrowness, this ridge looked somewhat like that caused by a gubernaculum. It was tagged by means of thread; then it and that part of the bursa distal to the testis and the attached "ligament" were excised as a unit and placed in fixing fluid.

In microscopic studies of transverse sections of the bursa, the four layers of its wall were observed. The most distinct ones were the peritoneal and the cremasteric. Since a gubernaculum, like a testis, is a retroperitoneal structure, the internal spermatic layer is

*This orifice should not be called the internal inguinal ring because the latter term is almost universally used for the purpose of designating a ring of transversalis fascia at the upper end of the inguinal canal. Incidentally, most authors who report cases similar to ours use such general terms as hernial sac for referring to the four-layered sac which contains the testis. The term "inguinal bursa" is useful for conveying the idea that the sac represents the anomalous persistence of a normal one of the fetus.

the one which should be expected to contain it. Despite most careful search, no trace of a gubernaculum could be found.

Transverse sections of the tissue tagged by means of thread (asterisk, Fig. 2) showed that the ridge of peritoneum observed during surgery was caused by blood vessels in the subperitoneal layer (tunica vaginalis communis or internal spermatic fascia). Fig. 3 illustrates this point.

A block of tissue including the fundus of the bursa and the upper part of the attached "ligament" (*x y*, Fig. 2) was sectioned serially and vertically. The sections showed that the "ligament" consisted of areolar tissue, fat, and small blood vessels. Its upper end fanned out to become a uniform spray of filaments, the spray being most conveniently described by comparing it to that of a garden hose. These filaments united with the fundus of the bursa by blending with the outer layer (external spermatic).

In considering this case, it is clear that the "ligament" created by blunt dissection should not be called the gubernaculum testis. On the posterior aspect of the internal spermatic layer of the bursa where a gubernaculum, if present, should be expected to lie, none could be found. Although these observations should not be taken to mean that in all patients with undescended testis a gubernaculum cannot be identified, they are evidence against the common notion that a place to look for one is below the bottom of the bursa.

The question arises as to whether the testis (left) had descended before birth and then had ascended after birth, a phenomenon which occurs normally in the rhesus monkey (Wislocki, 1933). This question cannot be answered because of a lack of records of pertinent observations on the patient during infancy. However, it may be pointed out that the presence of the bursa at the time of orchiopexy does not constitute evidence that at one time the testis had actually reached the scrotum because normally the bursa originates before the testis begins to descend. In a seven-month fetus in which one testis had already descended and the opposite one had not, the bursa on the side of nondescent had become a sizable structure (Wells, 1943).

Assuming that the left testis had not at any time reached the scrotum, might it be that agenesis of the gubernaculum had been the causative factor? This is most unlikely because at orchiopexy the testis was in the bursa and because it would seem that in the fetus the two main functions of the gubernaculum are to widen the orifice of the bursa and to steer the testis into it (Wells,[21] 1944). It is more reasonable to suppose that the gubernaculum had existed before birth and had become unrecognizable after birth, as in normal development.

As to why the left testis lay above the external inguinal ring, any view that the gubernaculum had failed to pull it into the scrotum may be rejected because of a lack of acceptable evidence that normally the gubernaculum actually exerts traction upon the testis (Forssner, 1928). In fact, in rodents, severance of the gubernaculum is followed by descent of the testis in a large majority of the cases (76 per cent, Wells,[22] 1944).

The fact that this was a case of bilateral cryptorchidism points to hormones as the causative factor. It would seem that during prenatal life the testes had failed to reach the scrotum because of failure of the androgen of pregnancy to cause the bursae to grow as rapidly as in normal fetuses. Several

observations support this view: (1) in certain patients with undescended testis, therapeutic injections of androgen are followed by descent (Hamilton, 1941), (2) in primates the urine of pregnancy contains androgen (Hain, 1939; Dorfman and Van Wagenen, 1941), (3) in rodents during postnatal life, injections of androgen cause rapid growth of the bursa (Wells,[23] 1944), (4) in unborn rats the size and number of the interstitial cells of Leydig may be increased experimentally by injecting gonadotropin under the skin (Wells,[24] 1946), and (5) in experiments in which unborn rats are deprived of their testes, or are subjected to this operation and then given pellets of androgen (subcutaneously), the data seem to indicate that the fetal testes produce a hormone (androgen) which accelerates the growth of such accessory reproductive organs as the seminal vesicles (Wells,[25] 1946). We are not aware of any observations which indicate that the gubernaculum is influenced by hormones.

There remains the related question as to why the testes had failed to enter the scrotum during puberty, or to enter it in response to the therapeutic injections of gonadotropin. Doubtless the answer is that by the beginning of puberty the external inguinal rings were too small and too unyielding to permit descent. As mentioned, this was true of the left ring at the time of orchiopexy. Neither above this ring nor below it were there any bands of fibrous tissue that might have prevented a descent of the left testis.

In conclusion, we were unable to identify a gubernaculum in any of four selected patients who were subjected to orchiopexy. The notion that in such patients it may be found below the fundus of the inguinal bursa is due to a misconception of it. If present, it should lie on the posterior aspect of the bursa and in the internal spermatic layer.

It is a pleasure to acknowledge our indebtedness to Dr. Owen H. Wangensteen who placed certain patients at our disposal, to Professor Edward A. Boyden who assisted in many ways but especially in planning the illustrations, and to Mrs. Dorothy N. Highby, senior laboratory technologist, who made the microscopic preparations.

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SOME OBSERVATIONS ON THE USE OF CURARE IN THE TREATMENT OF TETANUS

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CURARE, until the past several years, has been regarded as a pharmacologic curiosity, rather than a therapeutic agent. Its clinical application has been attempted from time to time but because the available preparations were of variable potency and there appeared to be a narrow margin between the dose necessary for the desired therapeutic effect and that which caused respiratory failure, its use in the treatment of disease was regarded as hazardous. The recent introduction of specimens of greater purity and standard potency has revived interest in the drug and stimulated investigation of its efficiency in diseases of the neuromuscular system. The activity of curare is due to various alkaloids but particularly to the presence of the alkaloid, d-tubocurarine, a crystallizable substance. Crude curare contains hydrolyzable resins, some of which give rise to undesirable side effects and toxic reactions. Through the efforts of Richard Gill, in cooperation with the research departments of certain pharmaceutical concerns, preparations of curare of standard potency, devoid of noxious substances, are now available. Two preparations generally employed for clinical use are Intocostrin, which is the crude drug freed of resins and toxic substances, and tubocurarine an aqueous solution of the active principle itself. Both are prepared so that a given specimen possesses standard potency. Intocostrin is widely used as an adjunct to general anesthesia to secure relaxation of the abdominal muscles. It is also extensively used to soften the convulsive phase in the metrazol treatment of psychoses. Scattered reports, some favorable, have appeared regarding its use in treatment of diseases of the neuromuscular system, particularly when these diseases are characterized by spasticity and hypertonicity of the muscles.

One disease in which its use has been suggested is tetanus. The idea of using curare in tetanus is not new. Numerous reports have appeared in the literature from time to time, some as early as 1860. On the whole, the use of curare in the treatment of tetanus has up to the present time been disappointing and unsuccessful. The poor results have largely been ascribed to the uncertainty of composition and the variability of potency of the preparations of the drug. The possibility that the newer and more refined preparations, such as intocostrin, might be more successful than the older preparations leads us once again to observe its behavior in this disease.

It is obvious to one familiar with the pharmacology of curare and the pathologic physiology of tetanus that the drug can afford little more than symp-

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tomatic relief in this disease. Curare exerts its action by blocking impulses to skeletal muscle at the endings of the somatic nerves. Apparently, it inhibits the action of acetylcholine at this point. Death from overdosage is usually ascribed to asphyxia from paralysis of the respiratory muscles. Recent experimental observations and clinical experience indicate that this premise is not strictly correct. Death has been known to occur from circulatory failure. In tetanus the usefulness of curare would be limited to overcoming the muscle spasm. The underlying cause of the disease would remain to be treated by antitoxin, penicillin, or other measures.

A nicotine-like action on the automatic ganglia may also be observed. However, this action appears to be of little concern clinically because the dose necessary to cause it is larger than that which causes paresis of the skeletal muscles. In addition, a histamine-like action is occasionally encountered.

The following are some observations made in five patients in whom the diagnosis of tetanus was established.

METHOD OF STUDY

The aqueous solution of curare, known as intocostrin,* containing twenty units of standard curare per cubic centimeter, was used undiluted in all cases. Resuscitating equipment for artificial respiration and for administering oxygen was available at the bedside at all times. Curarization was supervised by a physician member of the anesthesia department who remained in constant attendance throughout the entire therapy. Prostigmine, which to a certain extent antagonizes the curare action, was held in readiness for intravenous administration in the event of overdosage. The recommended dose of one-half unit per pound of body weight was computed in each case and this amount was not exceeded at any one time.

CASE REPORTS

CASE 1.—A 25-year-old colored woman complaining of stiff neck and trismus of two days' duration was admitted to the hospital. There was no history of trauma. The patient was well developed, in a good state of nutrition, and appeared to be mentally clear. Physical examination revealed fever (104° F.), trismus, rigidity of the neck and abdominal muscles, and hypertonicity of the muscles of the extremities. No puncture or other wound could be demonstrated. Blood, urine, and spinal fluid examinations revealed nothing significant. A diagnosis of tetanus was made.

Upon admission, tetanus antitoxin was administered, 100,000 units intravenously and 200,000 units intraumuscularly. In addition, phenobarbital, gr. 1½, was given intramuscularly every four hours. Eight hours after admission, the anesthesia department was consulted regarding the use of curare to alleviate physical exhaustion from the muscle spasm. Intocostrin was administered intravenously at the rate of 20 units per minute until 60 units had been injected. An average of two minutes was allowed to elapse between the injection of each cubic centimeter of solution. The jaw gradually relaxed over a period of five minutes from the time the injection was started and the rigidity of the neck diminished. The abdominal muscles remained rigid, however, and the extremities were still hypertonic. The reflexes decreased in activity, but remained active. After three minutes an additional 20 units of intocostrin were administered slowly over a period of two minutes.

*Supplied by E. R. Squibb & Sons, New York, N. Y.

This was followed by relaxation of the back and abdominal muscles. The muscles of the neck and jaw in the meantime became completely flaccid. After several minutes more the amplitude of thoracic excursions became markedly diminished. The diaphragm still remained active. Soon the diaphragmatic movements diminished and cyanosis of the mucous membranes and nail beds appeared. There was definite embarrassment to respiration necessitating the use of oxygen by mask. The pulse and blood pressure remained unchanged, however. Pulmonary ventilation became further embarrassed by obstruction caused by relaxation of the tongue. The tongue was supported by a rubber oral airway. The patient appeared drowsy, apathetic, did not respond to stimuli, and was unable to talk or swallow. The flaccidity gradually lessened, and diaphragmatic activity began to return. Within thirty minutes the trismus and rigidity of the back and abdominal muscles had returned. The status of the muscular system appeared no different than before curarization. The patient was again aware of her surroundings and was alert. Pulse and blood pressure did not vary significantly during the entire period of curarization.

Forty-five minutes after the completion of the injection of the first dose, 80 units were again administered intravenously over a period of twelve minutes. The sequence of events was similar to those following the first dose. However, the state of muscle relaxation and flaccidity lasted only twenty minutes this time. Eighty units were then administered intramuscularly in one dose. The flaccidity gradually reappeared and was maximal in fifteen minutes; it lasted approximately thirty minutes.

During the relaxation induced by the second and third injection, considerable mucus and saliva accumulated in the pharynx. The patient was unable to swallow these secretions because of the loss of control of the pharyngeal muscles and the muscles of deglutition. The secretions interfered with the airway unless frequent suctioning was practiced. This appeared to be an objectionable feature of the therapy as it markedly increased the hazard of asphyxia in the face of the diminshed ventilation due to paresis of the intercostal muscles and diaphragm. In view of the fact that a partial or graded response could not be obtained and the amount necessary to obtain relaxation caused complete curarization, no further use of the drug was attempted and therapy was continued by means of sedatives in conjunction with the antitoxin. The temperature came down by lysis, the muscle spasm gradually disappeared, and the patient left the hospital free of symptoms after three weeks.

CASE 2.—A 25-year-old colored man was admitted to the hospital complaining of pain in the jaws, stiffness of the extremities, and inability to open the mouth for ten days. Symptoms developed several months after he lacerated the right index finger. Physical examination revealed trismus, the classical risus sardonicus, generalized rigidity of the back and neck muscles, and opisthotonos. Temperature was 104° F. and he was semicomatose. No significant changes were noted in spinal fluid and urine or blood studies. A diagnosis of tetanus was made.

One hundred thousand units of tetanus antitoxin were administered intravenously and 40,000 intramuscularly upon admission. Phenobarbital, gr. 3, was given intramuscularly every four hours. Eight hours after admission, intocostrin was administered intravenously at the rate of 20 units per minute. Forty units caused a relaxation of the jaw and disappearance of the trismus. This amount was augmented in an effort to relax the muscles of the abdomen and lower extremities. Seventy units were required to effect relaxation of the muscles of the extremities. The intercostal muscles by this time lost their activity and respiration became diaphragmatic. The power of deglutition and phonation was lost and saliva and mucus accumulated in the pharynx. As in the previous case, the decrease in pulmonary ventilation caused anoxemia which necessitated the use of oxygen. The effect of the curare lasted approximately forty minutes after which time the spasticity and hypertonicity of all the muscles returned and appeared to be of the same intensity as before curarization. In view of the fact that the dose necessary to cause relaxation of the extremities was sufficient to cause almost complete cessation of the respiratory movements, no further curarization was attempted at this time. Ten hours later the patient was completely exhausted from the marked spasticity. It was decided to give the drug another trial. The lower extremi-

ties were rigid. Seventy units of intocostrin were again administered intravenously in divided doses over a period of five minutes. As before, complete paralysis of the muscles of the cranial, cervical, and spinal segments was obtained before any appreciable loss of tone of the muscles of the extremities was apparent. The effect lasted thirty minutes. The hypertonicity and spasticity reappeared and returned to apparently the same intensity as before the administration of the drug. Seventy units were again administered, but this time intramuscularly in a single dose. Within fifteen minutes the muscles of the upper extremity were completely flaccid. The powers of deglutition and phonation were gone; there was a notable diminution in thoracic and diaphragmatic activity. The lower extremities continued to be spastic at all times, however. Forty-five minutes after the administration of the drug, hypertonicity and rigidity reappeared in the muscles of the head and neck. No further attempt at curarization was made because it was obvious that the dose necessary to relax the lower extremities in this case could be obtained only by complete curarization and respiratory paralysis. Treatment was continued with hypnotics and the patient recovered.

CASE 3.—A 63-year-old colored woman was admitted to the hospital complaining of stiffness of the jaws and rigidity of the muscles for ten days. The portal of infection was a puncture wound caused by a splinter in the right heel. Details of the history were vague. Trismus and rigidity of the neck and back muscles were pronounced. She appeared to be well nourished and alert. With the exception of the neuromuscular findings, no abnormalities were noted upon physical or laboratory examinations. A diagnosis of tetanus was made.

She was given tetanus antitoxin, 60,000 units intravenously and 40,000 intramuscularly. In addition, phenobarbital, gr. 1½, and amytal, gr. 1½, were given intramuscularly every four hours during the first day. Oxygen by nasal catheter was also given. Twenty-four hours after admission, because there appeared to be little change in the neuromuscular status, curare was requested. Intocostrin, 40 units, was given slowly over a period of several minutes. Ptosis, heaviness of the lids, and relaxation of the muscles of the head and neck gradually appeared. The muscles of the abdomen became relaxed and the intercostals inactive. Respiration became diaphragmatic in type, jerky, and ceased after several minutes. This was approximately five minutes after the injection of the drug. Artificial respiration was instituted immediately by intermittent positive pressure with oxygen by means of an anesthesia machine. During this period, the airway became obstructed with mucus which, as in the previous cases, had accumulated in the pharynx. This was easily and quickly removed by applying suction. During this interval, however, the pulse became slow, weak, and at one time imperceptible. Blood pressure was not recorded at this time. Prostigmine (2 c.c. of 1:2000 solution) was given intravenously to antagonize the curare effect. After an estimated period of five minutes, the pulse became perceptible, then stronger, soon regaining its former quality and becoming of good volume. Diaphragmatic breathing became re-established as the effects of curare wore off. The spasticity and rigidity of the muscles returned. One hour after the administration of the drug respiration became labored and jerky and the pulse became irregular and finally imperceptible. Severe gasping respirations and respiratory failure followed. Artificial respiration was immediately instituted and continued for approximately fifteen minutes. The heart sounds were inaudible, the pulse was not palpable, and blood pressure was unobtainable. The mucous membranes were cyanotic, pupils widely dilated, and skin cold and clammy. Metrazol was given intravenously. This was followed by intracardiac adrenalin. After several more minutes the futility of employing further resuscitative measures was recognized and the patient was pronounced dead. Permission for a post-mortem was not granted. It was impossible to determine from the sequence of events whether death was due to the effects of the curare, either directly or indirectly, or to some other factor incidental to curarization. It was our feeling that indirectly it was due to curarization.

CASE 4.—A 36-year-old white man was admitted to the hospital eight days after receiving a laceration over the right eye following a fall from a ladder. The day before admission, he developed pain and stiffness in the jaws. He was treated with tetanus antitoxin

intramuscularly for four days. During this time, in spite of heavy sedation with barbiturates and the use of tetanus antitoxin, the muscle spasm appeared to increase in severity and became more generalized. On the fifth day, it was decided to alleviate the spasm with curare. Intocostrin was administered intravenously at the rate of 10 units per minute. Sixty units in all were given at this time. The jaws slowly relaxed. Within five minutes, after completion of the injection, the effect of the drug appeared to be well established. The abdominal muscles and muscles of the lower extremities remained rigid, however. An additional 20 units were given. The ankle clonus, which had persisted, now disappeared, but the powers of deglutition and phonation disappeared also. Thoracic movements became depressed although the diaphragm remained active. Saliva and secretion accumulated in the pharynx in spite of the administration of 0.5 mg. atropine intravenously before curarization. Forty minutes after the initial administration, the muscle tone began to return. In fifty minutes the muscles appeared to be as spastic as before curarization. Blood pressure and pulse varied little throughout the entire procedure. An additional 60 units were administered intravenously in the same manner but at a slower rate than the previous injection. The time of administration was exactly one hour after the first injection. Within five minutes, the relaxation was complete. The intercostal muscles were inactive, the powers of deglutition and phonation were absent, and the extremities were relaxed. Saliva and secretions appeared again in copious amounts. One hour later, the tone of the muscles began to return. The patient remained quiet. The dose was not repeated as in the previous cases because the amount necessary to cause an appreciable loss of muscle tone caused respiratory depression. Gradually the patient became restless. Five hours later there was marked excitement and intense spasticity of the muscles. Sixty units were again administered intravenously in the same manner as previously described. The behavior was similar to that after the previous injection. The response lasted fifty minutes this time. The dose was repeated again and similar results were obtained. Each administration was followed by marked respiratory depression in this subject. In view of this and the experience with Case 3, curarization was discontinued.

CASE 5.—A 24-year-old colored man was admitted to the hospital complaining of pain upon swallowing. The day before admission, he developed pain and stiffness in the jaws. Physical examination revealed trismus, stiffness of the neck muscles, and rigidity of the abdominal muscles. A diagnosis of tetanus was made. He was given tetanus antitoxin, both intramuscularly and intravenously, and phenobarbital at four-hour intervals as in the previously described cases. Approximately twenty-four hours after admission curarization was attempted.

Intocostrin was administered slowly intravenously at the rate of 10 units per minute. Eighty units were necessary to produce any notable effects. The jaws slowly relaxed. Within four minutes after completion of the injection, the effect of the drug appeared to be well established. The intercostal muscles became progressively less active. The diaphragm, likewise, decreased in activity. Within five minutes after completion of the injection of the drug there was complete cessation of respiratory efforts. Artificial respiration was instituted by means of intermittent positive pressure. The skin was cold and clammy. The pulse remained unaltered. There was no notable change in blood pressure. Diaphragmatic activity began to return twenty minutes later but because movements were ineffective in maintaining adequate pulmonary ventilation, the artificial ventilation was continued. The intercostal activity became fully established one and one-half hours later. Power of deglutition returned after two hours. It seemed unwise in the face of the response obtained to repeat the administration of the drug.

DISCUSSION

Although one cannot pass upon the merits and demerits of curare in the treatment of tetanus from the experience of the foregoing cases, it is obvious that the therapy as conducted in the patients was not without hazards and pos-

sesses certain drawbacks. First and foremost is the objection that the action of the drug was of short duration. Repeated doses were necessary at frequent intervals to maintain a sustained effect. This would not be a drawback if almost complete curarization had not followed each attempt to obtain the degree of muscle relaxation deemed to be of clinical value. When curare is used as an adjunct to inhalation anesthesia the loss of muscle tone appears to be in proportion to the amount of drug used. This graded response was not obtained in these patients. Instead the effect appeared to be abrupt in onset rather than gradual and the muscles became flaccid shortly after the loss of muscle tone became apparent. Even though the curare was administered slowly in divided doses the decrease in muscle tone was not apparent until the amount which caused flaccidity of muscles had been administered. Moreover the various groups of muscles were not affected simultaneously. The quantity of drug sufficient to relax the muscles of the head and neck did not necessarily affect the muscles of the lower back or abdomen. The fact that curare affects structures innervated by the cranial and cervical nerves before those innervated by spinal nerves was well demonstrated by these patients. The dose necessary to relax the more resistant groups of muscles innervated by the lower spinal nerves caused paralysis of the muscles supplied by the cranial nerves. The secretion of saliva and mucus continued, but, due to the loss of power of deglutition, accumulated in the pharynx. The pharyngeal muscles became relaxed, the tongue sagged backward into the pharynx, and, together with the mucus, caused partial obstruction to the airway. Pulmonary ventilation was further embarrassed by paresis of the intercostal muscles. Respiration invariably was gasping and jerky. The possibility of obstruction coupled with diminished ventilation was a hazard which was experienced with each administration of the drug. Theoretically, respiratory failure should be adequately cared for by artificial respiration. However, tetanus is a serious disease in which considerable stress is placed upon the respiratory and circulatory systems by the rigidity and convulsive spasms as well as the infection. Respiratory failure under these circumstances can be disastrous. Furthermore, recent experimental studies in dogs indicate that death occurs after protracted use of curare even in the face of adequate pulmonary ventilation.* Presumably it is the result of circulatory failure. In view of the hazards involved, constant attendance of the physician directing the therapy is mandatory. Although this is not too much to ask to save a life, it often happens that such arrangements are not always possible.

The suggestion has been made that the drug be administered in small doses at less frequent intervals without attempting to overcome completely the spasm and obtain "normal" muscle tone. This technique has been employed in various types of myotonias and spastic diseases with some degree of success. However, the promptness with which rigor, trismus, and other manifestations of hypertonicity returned as the effects of the drug diminished seems to preclude this as a possibility.

*Perlstein, M. A., and Weinglass, A.: Fatal Effects of Prolonged Complete Curarization, Am. J. Dis. Child. 67: 360, 1944.

In most instances the drug was given while the patient was receiving barbiturates. On three occasions, in three of the cases the sedation was withheld and the curare used alone. No appreciable difference was observed.

SUMMARY

Curare (intocostrin) was given to five patients in whom the diagnosis of tetanus was made for the purpose of alleviating convulsions and muscle spasm. Relief from the spasm was not obtained until the dose which caused almost complete curarization was given. The response was fleeting, lasting in most instances twenty or thirty minutes, after which time it was necessary to repeat administration of the drug. In addition, respiratory depression and obstruction were avoided with difficulty. One patient died one hour after administration of one single dose of curare which had been followed by respiratory and circulatory failure. Although the cause of death was not determined in this case it was believed to be caused by the curare.

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PULMONARY CYSTS

Special Reference to Surgical Treatment of Emphysematous Blebs and Bullae

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PULMONARY cysts, a pathologic entity that includes abnormal localized distentions of the various portions of the tracheobronchial tree and other discrete sacs originating from the interstitial portion of the lung are found in increasing numbers today because of the wider use of routine roentgenologic examinations of the thorax.

Bartholin, in 1687, reported the first recognized case. Since that time many have been reported. Koontz[1] in 1925 reviewed the medical literature and found presentations of 105 cases and in 1937 Schenck[2] found reports of 381 cases.

However, the term "pulmonary cyst" has been used to designate a wide variety of pathologic entities, thereby creating confusion concerning the clinical terminology. Various pulmonary lesions have been included in this group: congenital pulmonary cyst, cystic bronchiectasis, epithelized cavities following pulmonary suppuration, pneumatocele (localized alveolar or lobular actasia), chronic interstitial pneumonitis with emphysema, emphysematous bullae, and pulmonary blebs.

It, therefore, becomes evident that when one mentions pulmonary cyst, strong consideration should be given to its etiology, pathogenesis, and clinical picture rather than to discuss pulmonary cysts as a homogeneous group. Emphysematous blebs and bullae have come to our attention on occasion and, unlike congenital cystic disease of the lung, little has been written concerning their surgical management.

It is, therefore, the purpose of this paper to present five cases: three emphysematous bullae, one subpleural bleb, and one chronic interstitial pneumonitis with emphysema, four of which were treated by conservative surgery, and one by lobectomy.

ETIOLOGY AND PATHOLOGY

Although the precise mechanism of the genesis of pulmonary cysts is still unknown, it is generally admitted that they originate either from a developmental error or anomaly. Boyd[3] stated that there is such a great difference of opinion as to their pathogenesis that dogmatic statements are most unwise, but there are three probable origins: (1) congenital bronchiectasis, (2) dilatation of lymphangiomatous spaces, and (3) cyst formation in aberrant lung tissue or vestigial structures. The wall of the cyst may have the characteristics of

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bronchi, bronchioles, atria, infundibula, or alveoli, and the nature of the epithelium may be profoundly modified by the increase in the size or by the ballooning of the cyst as well as the presence of infection.

According to Miller[4] the manner in which a bleb is formed is similar to that which takes place in an interstitial emphysema, namely, a rupture of the wall of an alveolus which allows the air to escape into the alveolar layer of the pleura. This occurs at a point where, from some cause, the elastic fibers in the alveolar wall have given way, possibly from having been stretched to the breaking point. The air extends along the pleura in the same manner that a dissecting aneurysm extends along the wall of an artery. He also found a well-marked emphysema in every case in which emphysematous blebs occurred.

In the case of a bulla, the alveoli are first dilated, then atrophy and rupture of the alveolar walls take place with a gradual formation of a bulla of greater or less size which communicates with a bronchiole or a larger division of the bronchial tree. In the case of a bleb, the pleura is separated by the air from the underlying alveolar walls. In bulla formation the pleura retains its connections with the lung, although the alveoli beneath it give rise to a bulla through rupture and fusion.

Grossly, in the first type, the pleura gives the sensation of a thin membrane which slides freely over the surface of the underlying substance. In the case of a bulla, it is not movable and the underlying space gives the impression of an air-filled cavity.

Although the emphysematous bleb and bulla have been included in the group of pulmonary cysts, they actually are two distinct entities. The wall of the former pathologic condition is lined by the surrounding alveoli and there is no true epithelial lining, while the latter has a definite bronchial epithelium. The bulla can be considered best as an advanced stage of a localized pulmonary emphysema.

Obstructive, processes of the bronchi caused by either intrinsic or extrinsic lesions will produce a hyperinflated bulla. As a result of a check-valve mechanism, however, the affected segment becomes blown up with air so that the bulla may reach huge dimensions which may rapidly increase or diminish in size and not infrequently disappear. Because of this valvular mechanism, constant intracavitary positive pressure may develop, giving rise to a picture which is described by many as pneumatocele.

CLINICAL PICTURE

Since emphysematous blebs and bullae are frequently associated with marked emphysema, the clinical picture may be that of the latter condition only. The symptomatology, however, depends on the size, location, valvular mechanism, condition of contiguous lung parenchyma, and changes that may take place in the intrathoracic pressure. Infection is rarely seen and plays no important role in masquerading the disease, unlike cysts of other types which are prone to infection and frequently cause symptoms of pulmonary suppuration.

Many cases are symptomless and unrecognized for long periods of time when the lesions are not sufficiently large. Often pulmonary blebs and bullae acquire large dimensions with marked compression of the surrounding lung and displacement of the mediastinum causing respiratory embarrassment. Dyspnea is then a prominennt symptom, the degree of which depends upon the patient's activity or exertion. The difficulty in breathing is not infrequently in the form of wheezing. Cough, expectoration, or pain in the chest, are frequent complaints. Occasionally the sputum may be blood streaked. Cough associated with wheezing may suggest a diagnosis of bronchial asthma.

Not infrequently a spontaneous pneumothorax resulting from a rupture of a pulmonary bleb or bulla is indicative of this condition as has been clearly demonstrated in patients reported by Oechsli and Miles.[5]

RADIOLOGIC FEATURES

Roentgenographic study presents the only evidence in the diagnosis of pulmonary bleb and bulla. The lung field shows a peculiar variation from normal. The shadows cast by these structures are usually circular or ring-shaped, sometimes linear vacuolated in type, simulating bronchiectasis. They appear in the roentgen plate as a large area of increased brilliancy, in the midst of which a few lung markings can be seen. The border of these annular shadows is represented by a fine, hairlike, thin and sharp area of increased density which differentiates them from the walls of a congenital cyst which are rather coarse and often finely frayed out.

A tension or localized pneumothorax can frequently be mistaken for either a bleb or bulla because both conditions show an area of increased brilliancy and lack of normal lung markings. However, in a large emphysematous bulla some compressed pulmonary tissue can always be seen either in the apex of the lung or in the costophrenic angle. Another differential feature is that in tension pneumothorax the lung collapses toward the hilus where it forms a prominence at its root.

TREATMENT

As previously mentioned, emphysematous blebs and bullae under certain conditions, such as check-valve mechanism with obstruction to the egress of air, will balloon out and acquire large dimensions. The mechanical effect upon respiration and circulation will then cause incapacitating dyspnea. Pulmonary blebs and bullae, even when large, can be asymptomatic and only discovered by x-ray examination; they frequently will disappear spontaneously. These patients are not candidates for surgery, no more than when they constitute only a part of generalized pulmonary fibrosis and emphysema.

The five patients that we report have all been operated upon because of respiratory distress to the degree of incapacitating them from leading a normal life.

OPERATIVE PROCEDURE

Operation can be performed under local paravertebral block with endotrachael intubation or under general anesthesia. Upon opening the pleural cav-

ity the cyst which is under pressure will immediately herniate through the pleural rent while the normal lung tissue will collapse because of the pneumothorax. The cyst may then increase in size with the administration of endotracheal positive pressure. Attempts to decompress the cyst manually are usually futile, proving the presence of a one-way valve mechanism. The cyst wall may be uni- or multilobulated. Not infrequently, discrete emphysematous

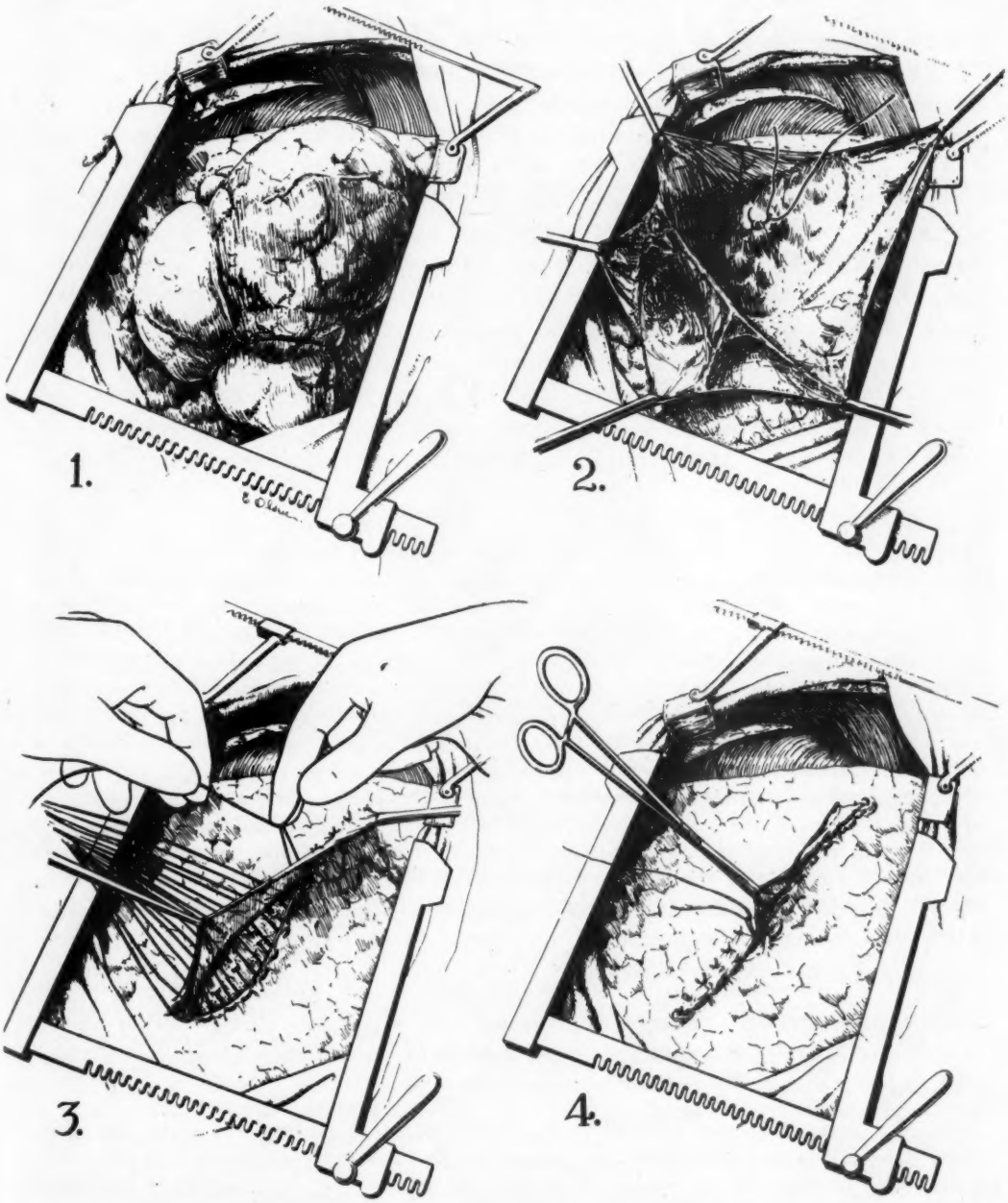


Fig. 1.—*1*, Pulmonary cyst visualized through operative incision; *2*, closing suture over bronchial orifice; *3*, imbricating sutures in visceral pleura; *4*, final closure with interrupted black silk.

changes can be seen in the periphery of the remaining lobes. One or more segments may be involved. The capsule is thin, glistening, and translucent. Upon opening the air-containing cavities, loose strands of fibrous tissue are encountered traversing the walls. The communicating bronchioles cannot always be found, even with the aid of increased intrapulmonic pressure. However, increased pressure delineates with relative accuracy the margins of the healthy lung. Bronchiolar openings, when seen, are closed individually with mattress silk sutures. Through-and-through mattress sutures are next placed at the base of the cyst through healthy lung tissue in order to obtain an airtight repair. At this time, saline solution is poured into the open cyst and the anesthetise is required to increase the intrapulmonic pressure so that air leaks may be detected and if present, are repaired. The walls of the cyst are then excised down to the previous suture line and the lung surface is pleuralized by suturing the edges of the removed cyst with interrupted silk. Little or no hemorrhage is encountered. Emphysematous lobules are sometimes present in a pedunculated form and can be easily removed by placing mattress sutures through their pedicles. The lung is again expanded for further detection of air leaks. The pleural surfaces are then rubbed with dry gauze in order to produce an obliterating pleuritis. A drainage tube is finally placed in the pleural cavity which is kept under negative suction for forty-eight hours to facilitate a rapid re-expansion of the remaining lung and obliteration of the pleural space.

CASE REPORTS

CASE 1.—J. H., a 50-year-old man, was a motorman. He had a history of chronic cough, progressive shortness of breath, and wheezing, for the past five years. Shortly previous to admission, the patient coughed and expectorated about two ounces of mucopurulent sputum and had pain in the right chest associated with marked dyspnea and wheezing. Examination of the chest revealed marked limitation of motion on both sides and an emphysematous type of chest. Over the region of the right upper lobe, breath sounds were very distant. X-ray examination on Sept. 4, 1943, revealed the left lung to be apparently normal. The upper right lung field showed an increased brilliancy and a marked reduction in pulmonary markings which suggested a large, thin-walled bleb or cavity. The right upper lobe was displaced toward the diaphragm as a result of the air-containing cavity. At operation on Dec. 3, 1943, excision and repair were done. A giant air-containing cyst was found in the right upper lobe filling approximately one-third of the volume of the right hemithorax. Posterior to the cyst, four small bullae were seen.

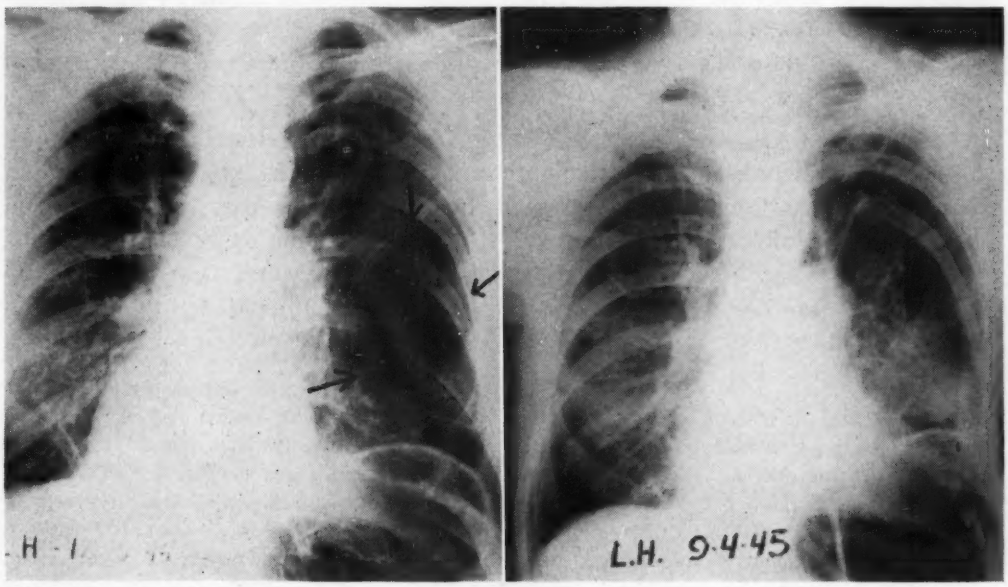
Microscopic Diagnosis.—Microscopic diagnosis was compatible with bullous emphysema.

Comment.—This patient was treated for asthma for many years because allergy tests proved him to be sensitive to house dust. Following operation, the patient was markedly relieved of dyspnea and wheezing. X-ray follow-up revealed a completely re-expanded upper lobe with no evidence of emphysematous changes.

CASE 2.—L. H., a man aged 58 years, a clerk, was admitted to the hospital December, 1944. Up until three years before, the patient was in apparent good health. At that time, while riding in a car, he was seized with a paroxysm of coughing and complained of marked shortness of breath which was progressive. There was no history of expectoration, hemoptysis, or wheezing. He had sinus trouble for several years. He also had a double, inguinal hernia repaired and megacolon, still present at the time of admission. Upon physical examination no abnormalities were found in the right lung. In the left lung there was an

absence of breath sounds over the lateral and posterior portions of the lung. Roentgenogram (see Fig. 2, *A*) of the chest on Dec. 19, 1944, showed a thin-walled, clear area at the left base which extended from the anterior to the posterior chest wall but did not include the costophrenic angle. There was no fluid present in the pleural cavity. The markings in the adjacent lung were somewhat thickened and, except for this, the lung appeared clear elsewhere. The mediastinum was displaced slightly toward the right and the left diaphragm was somewhat elevated, probably as a result of the megacolon. Bronchoscopy revealed an upward displacement of the left upper lobe bronchus with narrowing of the lower lobe due to extrinsic pressure. At operation Dec. 20, 1944, excision of emphysematous bleb was done. During operation many subpleural emphysematous blebs in the dorsal segment of the lower lobe and one very large in the lingular segment of the upper were seen. The lingular segment had a complete fissure line, creating a separate lobe.

Microscopic Diagnosis.—Microscopic diagnosis was emphysematous lung tissue consistent with subpleural bleb.



A. *B.*

Fig. 2 (Case 2).—*A*, Preoperative roentgenogram showing pulmonary cyst; *B*, postoperative roentgenogram showing absence of cyst with re-expansion of remaining lung tissue.

Comment.—This patient was referred to us because of progressive shortness of breath which prevented him from doing his work. Intrathoracic pressure symptoms were present as shown by roentgenogram and bronchoscopy. The operation relieved the patient of the symptoms. Follow-up x-ray picture (Fig. 2, *B*) showed re-expansion of the remaining lung with absence of emphysematous changes.

CASE 3.—J. R., a 22-year-old student nurse, was admitted to the hospital September, 1944, complaining of fatigue and some shortness of breath for quite some time, but these symptoms were not bothersome until two months before, at which time she complained of progressive dyspnea, slight cough productive of two ounces of mucoid sputum daily, associated with pressure sensations and soreness in the lower left chest region. During the two months previous to admission, she had noticed that the left costal margin was beginning to flare out. She was then admitted to the Boston City Hospital where a diagnosis of spontaneous pneumothorax was made. Upon reviewing roentgenograms taken one and one-half years before, the

same radiologic picture was found which was later interpreted as a congenital cystic formation of the left lobe. Examination of the left side of the chest revealed a slightly prominent left costal flare. Percussion note was hyperresonant and breath sounds were almost absent over the left lower lobe area. Breath sounds were also high-pitched and slightly suppressed over the left upper lobe. Bronchogram revealed a distorted left lower lobe bronchus with crowding of the bronchial branches. At operation on July 27, 1944, the lower lobe was found to be ballooned out, especially in the basilar segment. No anthracotic pigment could be seen in that segment, in contrast to the superior segment, which presented normal pigmentation. Diffuse hyperinflated lobules were found rather than one thin-walled, large, ballooned cyst as was suggested by the roentgenogram. A left lower lobectomy was performed. The gross specimen revealed about 90 per cent of the lobe to be made up of tensely distended lung, conforming to the shape of the chest wall. This portion was smooth, glistening, light pink-yellow, and was soft and spongy in consistency. At the apex and along the anterior portion of the medial aspect, there was a strip of gray-purple, noncrepitant, atelectatic lung tissue present. The cut surface revealed widespread, spongy lung parenchyma, involving about 95 per cent of the lobe. This segment consisted of diffusely dilated alveolar sacs which measured to 0.5 cm. across.

Microscopic Diagnosis.—Microscopic diagnosis was marked emphysema with peripheral atelectasis.

Comment.—Although no single, large bulla or bleb was found, the x-ray shadows were mistaken for a pneumothorax. The hyperinflated lobules caused the pressure symptoms and progressive dyspnea. Lobectomy was performed because of the diffuse involvement of the lobe. The postoperative x-ray examination revealed complete re-expansion of the left upper lobe without any evidence of emphysematous changes. The patient completed her training and is now symptom-free.

CASE 4.—J. D., a 44-year-old man, was a cobbler. Admitted to the hospital on March 12, 1945, the patient complained of cough, productive of slight amount of thin, mucoid sputum. At times the sputum was blood streaked. Progressive dyspnea associated with occasional wheezing was also present. The patient stated that three months previous to admission, he felt a bubble break in his right chest and he raised a large amount of sour-tasting, colorless material. This patient was diagnosed elsewhere as tuberculous. X-ray examination of the chest on March 12, 1945, revealed that in the left base there were present a few curved, gracile, linear shadows, suggesting air-containing cavities. On the right side, lung markings were absent above the second interspace anteriorly and the fifth rib posteriorly. The x-ray report was as follows: Possible pneumothorax pocket but the fine lines which formed the lower border of the area were more suggestive of a large emphysematous bulla. Right and left diaphragm were low in position. At operation March 14, 1945, excision and repair were done. In the right upper lobe a huge, emphysematous bleb was found almost replacing the entire lobe. There were also a few emphysematous lobulations in the middle lobe.

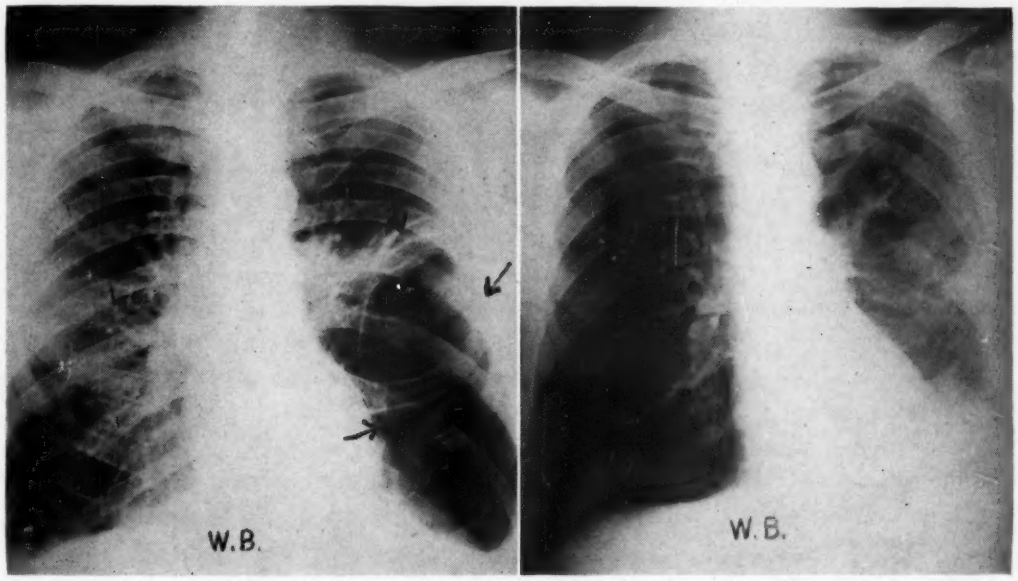
Microscopic Diagnosis.—Microscopic diagnosis was fibrous tissue with mesothelial lining consistent with emphysematous bleb.

Comment.—The x-ray appearance of the bleb could have been easily mistaken for an apical pneumothorax. This patient was diagnosed and treated for tuberculosis. Postoperative x-ray view showed complete re-expansion of the lung and as yet showed no evidence of progression of the emphysematous changes found during operation in the middle lobe. Patient at the present time is asymptomatic.

CASE 5.—W. B., a man aged 49 years, was a plumber. He was admitted to the hospital in August, 1945, complaining of progressive dyspnea on exertion and marked wheezing on

the left side which had been present for three years. Roentgenogram taken one year before admission revealed a large, air-containing cyst in the left lower side of the chest. X-ray view (see Fig. 3, *A*) upon admission revealed decreased density throughout the entire lower half of the left lung. Throughout this area many fibrotic strands were present, giving rise to a cystlike appearance. Lung markings in the superior portion of the emphysematous bleb appeared to be quite close together. The upper third of the lung showed no abnormality. The impression was that of emphysematous bleb involving the lower one-half of the left lung. Upon comparing both views, taken one year apart, a definite increase in the size of the cyst was noted. Physical examination revealed hyperresonance and absence of breath sounds in the left lower thoracic area. While in the hospital the patient developed an episode of coughing, wheezing, and cyanosis, which simulated a typical bronchial asthma attack. At operation Aug. 17, 1945, excision and repair were done. When the pleural cavity was opened a huge, balloon cyst immediately herniated through the opening, indicating the high intracavitary positive pressure.

Microscopic Diagnosis.—Microscopic diagnosis was emphysematous lung tissue, consistent with bulla.



A. *B.*

Fig. 3 (Case 5).—*A*, preoperative roentgenogram showing pulmonary cyst; *B*, postoperative roentgenogram showing absence of cyst with rexpansion of remaining lung tissue.

Comment.—This case was interpreted as bronchial asthma and treated accordingly, without benefit. The increase in the size of the pulmonary lesion and displacement of the mediastinum demonstrate the increase in positive intracavitary pressure which results from the check-valve mechanism. Postoperative roentgenogram (Fig. 3, *B*) reveals complete re-expansion of the lobe with disappearance of the emphysematous area. Patient has returned to work with no incapacitating symptoms.

CONCLUSIONS

1. Five cases of pulmonary emphysematous cysts, three bullae, one bleb, and one chronic interstitial emphysema involving the entire left lobe, are presented.

2. Emphysematous blebs and bulla, under certain conditions, are definitely incapacitated because of progressive dyspnea.

3. A simple, conservative type of surgical treatment, with excision of the involved area and preservation of normal lung tissue, is described.

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BRUCELLOSIS OSTEOMYELITIS

Report of Two Cases in Which Shafts of the Long Bones Were Involved

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SYSTEMIC brucellosis during the acute phase characteristically produces two outstanding symptoms, namely, fever of varying degree and generalized aching, especially in the lumbar portion of the spinal column and in the long bones. Might it not be reasonable to suppose that an embolus of species of Brucella could multiply in these bones to produce osteomyelitis? A search of the literature reveals substantial support for such a supposition, because there are numerous reports of brucellosis of the lumbar part of the spinal column, and an occasional record of a similar infection in other bones.

Since there are several excellent reports which describe brucellosis osteomyelitis in the lumbar portion of the spinal column, only brief mention of this particular lesion need be made herein. The few reported cases in which brucellosis osteomyelitis has involved bones other than the spinal column will be considered in more detail. Steindler[1] mentioned the largest series of recorded cases of vertebral infection; he said that up to 1939 fifty-seven cases had appeared in the literature. He also added four cases of his own, in which all signs pointed to infection with some species of Brucella. In only one of these four cases was the causative organism produced by culture of material taken from the lesion, since this single case was the only one in which the treatment was surgical, permitting of access to the lesion.

Kulowski and Vinke[2] summarized this single case of Steindler, which was the first instance of proved brucellosis osteomyelitis. Kulowski[3] also reported two cases of formation of abscess among ten cases of brucellosis of the spinal column. Generally, conservative treatment eventually yields fairly good results, as demonstrated by Steindler[1] and Phalen, Prickman, and Krusen[4] the latter of whom employed fever therapy with success for two of three patients.

Steindler[1] and Kulowski,[3, 5] in their overlapping reports, referred to several interesting cases of extraspinal osteomyelitis proved by culture to have a basis in brucellosis. One patient who had had osteomyelitis of the humerus for six years was cured by saucerization and establishment of drainage. In another case, after severe infection, the head and neck of a femur finally healed and the hip joint underwent complete ankylosis, with no treatment other than establishment of drainage. Cases of brucellosis osteomyelitis involving the skull and ribs, an ischium, and the bones of a hand also have been reported by Steindler and others associated with him. Hardy and associates[6] reported an instance of brucellosis osteomyelitis of the shaft of the humerus. O'Donoghue[7] described a case in which brucellosis osteomyelitis involved a femoral head. Ankylosis of

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the hip with complete healing occurred after the establishment of surgical drainage. Conservative treatment as employed by Gardner and associates[8] produced cure of a patient who had periosteal abscesses of the tibia and swelling of the knees, of one rib, and later of the right forearm. The lesions were proved, by means of the results of biopsy and culture, to be those of brucellosis. Mazzini and Carman[9] of Argentina reported an instance of proved brucellosis of the femur. Two years after biopsy, the lesion was found to have remained active and possibly to have extended to the right humerus. A unique instance of brucellosis osteomyelitis of an exostosis in the lower femur was reported by Horstmann.[10] There are numerous references[1, 3, 5-7, 11, 12] to polyarticular infections in which the epiphysis may have been involved.

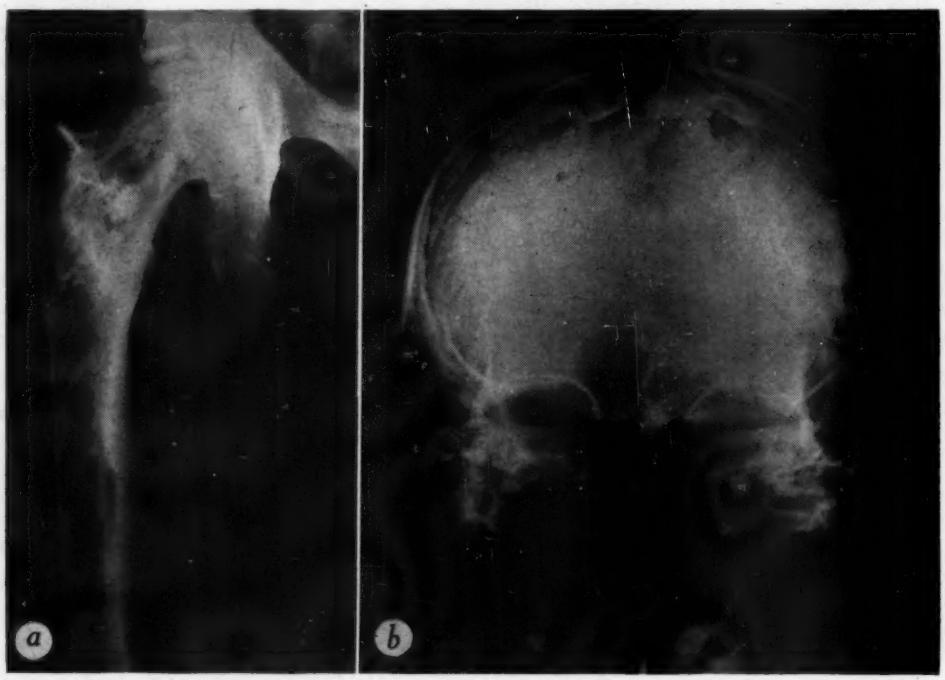

Fig. 1.—*a*, Roentgenologic appearance of the right hip and femur of the patient in Case 1 on July 20, 1933, one year after drainage of an abscess in the right femoral neck, showing thickening of the cortex, with abscess in the midfemur and opaque injected substance at the site of the abscess in the femoral neck; *b*, area of osteomyelitis in the right parietal region of the skull, on the same date as in *a*.

REPORT OF CASES

CASE 1.—A veterinarian 58 years old was first seen at the Mayo Clinic in 1932, complaining of pain in the left hip and a draining sinus situated high in the right thigh. In 1928, after he had removed a placenta from a cow at the birth of a calf, an infection had developed on his arm, and soon had involved a gland in the axilla. Results of a cutaneous test for the organisms of brucellosis several months later were positive. The arm and axilla healed within a few weeks, with no treatment.

In December, 1929, a sudden pain developed in the left hip. This persisted for approximately one month before it completely subsided. There was no fever during this period. A red, tender area appeared on the outer aspect of the right thigh in March, 1930, and was followed by a month of "flu." The red area was lanced in June, and had drained since that time.

Two months prior to the patient's admission, pain gradually developed in the left hip. It was aggravated by activity or pressure over the area. The patient lost fifteen pounds (6.8 kg.) in the two months prior to admission.

Results of physical examination were essentially negative, except for discovery of a draining sinus situated in the upper part of the right thigh and the testimony of pain at pressure over the left greater trochanter. The patient was not febrile and had not been during the preceding months. Results of a blood count were essentially normal: leucocytes amounted to 9,100 per cubic millimeter, the differential count disclosed that 70 per cent of the leucocytes were neutrophiles, 23 per cent were lymphocytes, 4 per cent were mononuclear leucocytes, 2 per cent were eosinophiles and 1 per cent were basophiles. Results of urinalysis and of flocculation tests of the serum were negative. Roentgenologic examination revealed a normal thorax and osteomyelitis of the right femur, with cystic areas of the right femoral neck, and of the left acetabulum and ileum.

On June 27, 1932, an abscess in the patient's right thigh was drained. A drill hole into the right femoral neck yielded a small amount of thick, yellow pus. It was felt that most of the symptoms over the left trochanter were based on bursitis.

About one year later an abscess posterior to the left greater trochanter was drained, and osteomyelitis in the right parietal region of the skull was detected by roentgen rays (Fig. 1, *a* and *b*). Results of agglutination tests for brucellosis on two occasions during this visit were positive in dilutions of 1:80, and material obtained from the abscess produced the organisms of brucellosis when it was cultured. There were no symptoms referable to the right hip, but the hip sinus continued to drain. The wound in the left hip healed rapidly.

In 1935 a roentgenogram revealed marked thickening of the cortex at the inner aspect of the upper part of the right femur, along with an old area of cystic destruction situated below the trochanter and in the femoral neck.

Despite the administration of vaccine and frequent courses of therapy with sulfonamide compounds, the lesions remained active. In a letter from the patient received in 1940 he reported that he had been in bed most of the previous year.

CASE 2.—A farmer 45 years old entered a hospital in November, 1945, complaining of fever and a swollen, painful red area over the medial aspect of the lower part of the left thigh.

For one month in 1925, the patient had had fever in which the temperature was as high as 104° F. (40° C.) with severe pain in the back and in bones. He had lost fifty-four pounds (24.5 kg.) during this illness. He reported that abortion frequently had occurred in cattle in his herd shortly before the onset of his fever. Although he had had no specific complaint, he said that his health never had been satisfactory since the fever. Detailed questioning revealed that he had had pain in the lower part of the left thigh for seven years, but that he had experienced it only when pressure was exerted over the area. Five weeks prior to admission, severe pain had developed in the lower and anterior part of the left thigh. Shortly thereafter temperature had increased to 103° F. (39.4° C.). Both fever and pain had continued.

Physical examination revealed a poorly nourished, flushed, feverish man who had a tremendously swollen, red area over the lower part of the left thigh. Other observations disclosed nothing abnormal except for a temperature of 100° F. (37.8° C.). Studies of the blood revealed that the result of a flocculation test of the serum was negative, that the value for hemoglobin was 13.4 Gm. per 100 c.c. of blood, that erythrocytes numbered 4,370,000, and that leucocytes numbered 14,700 per cubic millimeter of blood. Results of two agglutination tests were positive for the organisms of brucellosis in dilutions of 1:80. Marked osteomyelitis with sequestration in the lower part of the left femur was demonstrated in roentgenograms (Fig. 2, *a* and *b*).

Penicillin was administered for several days prior to performance of sequestrectomy. A large abscess, connected through a small cloaca with the region involved by osteomyelitis, was found in the anterior medial portion of the thigh. The pus from the abscess was thick and brown, and the bone marrow well along the femur had been replaced by a very thick cheeselike, yellow, highly odiferous material. A sancerization and a sequestrectomy operation

were performed. The wound was packed open with petrolatum gauze, and the knee held at rest with a Thomas splint. The patient began to carry out graduated knee exercises several days after the operation.

Microscopic studies of tissue removed at the time of surgery revealed subacute and chronic osteomyelitis with peculiar zones of caseous-like necrosis, and the pathologist noted that this was possibly on the basis of brucella infection. Results of both culture and examination of smears were positive for the organisms of brucellosis.

Fig. 2.—*a*, Anteroposterior, and *b*, lateral roentgenograms of the lower part of the left femur of the patient in Case 2 on Nov. 17, 1945, showing osteomyelitis with a large sequestrum; *c*, seven months (June 7, 1946) after the performance of sequestrectomy and a saucerization operation.

After operation, the patient received two courses of 2,000,000 units of streptomycin daily. The first course lasted for two weeks; the second was completed in one week, with a ten-day rest period between the two. Pain and fever disappeared immediately after the operation. No conclusion was drawn concerning the value of the streptomycin employed.

After the operation the amount of material drained gradually decreased, and the bone appeared to be healing slowly. The patient was seen in June, 1946 (Fig. 2, *c*), at which time moderate drainage was still present.

Small quantities of purulent discharge persisted until March 25, 1947, at which time the scar was excised and the sinus curetted thoroughly revealing healthy, bleeding bone. No brucellosis organisms were found after culture of the excised tract. Multiple small pieces of cancellous bone from the left ilium were placed in the bony defect. A plastic type of primary skin closure was then performed. There has been no sign of recurrence at the present time (Aug. 5, 1947).

COMMENT

The diagnosis of brucellosis of the shafts of long bones should not be difficult to make if the possibility of presence of the condition is constantly borne in mind. In nearly all instances, a history of relatively recent and obscure fever, with pain in bones and the lumbar part of the spinal column, will be obtained. However, since uncomplicated brucellosis osteomyelitis generally is of low virulence, it may be difficult in many cases to obtain a history of recent infection. Chronic osteomyelitis not accompanied by drainage, and producing little discomfort and disability, should be suspected of having a basis in brucellosis. Agglutination tests are of little value unless the results are strongly positive, since in most cases in which the disease is long standing, the titer is within the upper limits of normal. Frequently the pus is cheesy and grossly different from that associated with the usual pyogenic infection. Careful microscopic study will reveal a giant-cell type of reaction with irregular caseation, which may be confused with that of tuberculosis. When there is any suggestion of the presence of the aforementioned variations from the typical manifestations of classic osteomyelitis, material from the lesions should be carefully cultured. If the foregoing suggestions are carried out, many more instances of brucellosis of the bones should be detected than have been found in the past.

Probably a saucerization operation preceded and followed by the use of penicillin in an attempt to prevent secondary infection will yield the best results in brucellosis osteomyelitis other than that of the spinal column. When brucellosis osteomyelitis of the spinal column is present, conservative treatment should be in order, unless actual formation of abscess has occurred. The value of streptomycin in the treatment of brucellosis osteomyelitis remains to be evaluated.

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CIRCULATORY CHANGES PRODUCED BY CLAMPING OF THE THORACIC AORTA

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SURGICAL excision of the anomalous segment of aorta for treatment of congenital coarctation of that vessel was reported in 1945 by Crafoord and Nylin[1] and Gross and Hufnagel.[2] Clamps were applied to the aorta above and below the usual site of coarctation at the *ligamentum arteriosum*. The proximal clamp was applied just distal to the left subclavian artery so that circulation to the head and upper extremities was unimpaired. Blood flow distal to the clamps was maintained through collateral channels around the obstruction. After the constricted segment of aorta had been excised, continuity of the vessel was re-established by end-to-end anastomosis. In the first human being operated upon by Gross, immediately after the clamps were released, the heart went into uncontrollable dilatation and the patient died.[2, 3, 4] Gross thought that the failure was caused by inadequate return of blood to the heart after the clamps were released. In his subsequent operations the clamps were released slowly over a period of minutes with the patient in the Trendelenburg position. The rate of blood infusion was increased during the period of unclamping. After these precautions were adopted, no further deaths were reported. Concerning the cause of heart failure, Gross said,[4] "From some of our experimental work, and from a disastrous outcome in one case, it is evident that a quick removal of the last aortic clamp may impose a momentary but serious burden on the cardio-vascular apparatus. The sudden opening up of an enormous vascular bed in the lower part of the body makes great demands upon the heart. The cause of death in the first patient has been loosely described as 'cardiac collapse' since the exact mechanism of failure is not known. Presumably, it was a form of 'shock' because blood flowed rapidly into the depleted system in the lower two-thirds of the body, pooled there, and did not return quickly enough to supply the heart with a circulating medium."

Crafoord had not observed such cardiac failure despite experience with the aortic occlusion maneuver both during excision of coarctation and during division of patent ductus arteriosus.[5] In view of the added strain imposed upon the heart by such obstruction, and the abnormal conditions which must prevail immediately after release of the clamps, the following experiments were carried out in an effort to determine whether the failure could be explained by existing concepts or whether factors hitherto undescribed played a part.

EXPERIMENTAL

Methods.—Ten mongrel dogs of varying age and sex were used. The weight of the animals varied from seven to fifteen kilograms. Nine of the ani-

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mals were anesthetized with nembutal given intravenously in doses of 30 mg. per kilogram of body weight. One of the animals was anesthetized with cyclopropane and oxygen in a closed circuit with a soda lime cannister. The trachea was cannulated in each animal. In animals anesthetized with nembutal, during the period when the chest was opened widely, respiratory exchange was maintained by intermittent blasts of compressed air delivered by a mechanical respirator. In the animal anesthetized with cyclopropane, respiratory exchange was maintained by rhythmical pressure on the breathing bag of the anesthetic machine. No preoperative medication was given to the animals anesthetized with nembutal. The dog treated with cyclopropane received 30 mg. of morphine sulfate by subcutaneous injection during the immediate preoperative period.

The animal was placed in the dorsal decubitus on an animal board which was horizontal in all but one of the experiments. The trachea was cannulated in the neck. The internal mammary arteries were drawn up into the neck incision with an aneurysm hook, and ligated. The anterior part of the chest wall was then removed by incision at the costochondral junctions with minimal loss of blood. The end arterial pressure in the left carotid artery and left femoral artery was measured by mercury manometer. A 15 gauge hypodermic needle was inserted into the superior vena cava a few millimeters above the atrium. The needle was directed toward the heart. The needle was connected to a small-bore manometer containing 0.5 per cent heparin in physiologic saline solution. Venous pressure readings were taken visually and the time of reading was indicated by a mark on the kymograph drum. Care was taken that the needle did not come in contact with the sinus area. In some of the animals volume changes in the leg and in a segment of small intestine were measured by plethysmograph connected to a recording water manometer. The thoracic aorta was mobilized distal to the origin of the left subclavian artery and obstructed in continuity with a clamp similar to the one described by Gross and Hufnagel.[2] Care was taken during the application of this clamp that it did not press upon the vagus nerve or left pulmonary artery. During one experiment arterial blood samples were analyzed for pH with the glass electrode and for lactic acid by the colorimetric method of Barker and Summerson.[6]

Results.—Immediately after clamping the aorta there was a rise of carotid arterial pressure; the increment amounting to 40 to 60 mm. of mercury. The response illustrated in Fig. 1 is typical except that in most of the records the rise of arterial pressure was prompt and sustained. Femoral pressure fell rapidly. Although all pulsations were eliminated from the femoral artery tracing, the pressure did not fall to zero but stabilized at around 20 mm. of mercury. There was a pronounced slowing of pulse rate, which was probably due to the rise of arterial pressure in the carotid and aortic reflexogenic areas. The slowing was less pronounced under nembutal anesthesia than under cyclopropane anesthesia. During this period the heart visibly increased in size, and contractions seemed more vigorous.

In all experiments there was a rise of venous pressure after application of the clamp. The rise varied from 5 to 50 mm. of saline solution. The rate of

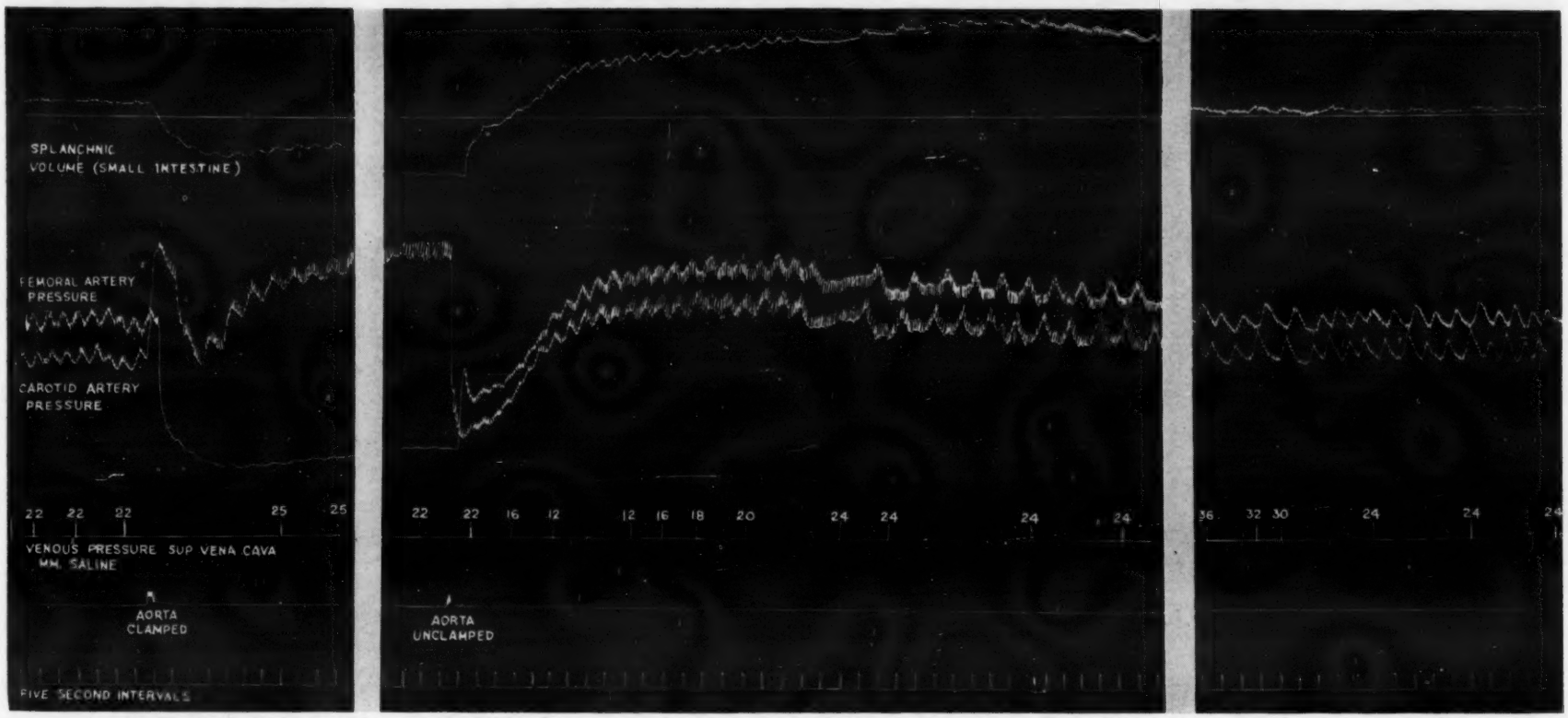

Fig. 1.—Response to rapid clamping and unclamping of the aorta in a dog under nembutal anesthesia. The first break in the record represents an interval of 5 minutes. The second break represents an interval of 1.5 minutes.

rise was variable, occasionally rising promptly to a plateau and occasionally showing progressive elevation throughout the entire period of obstruction. Uniformly there was a fall in the volume of enclosed small intestine. The fall of volume continued throughout the period of clamping. Leg volume recording showed little change (probably due to lack of sensitivity in our apparatus). One or two of the records showed slight reduction in the volume of the leg following application of the clamp, but such a change was so slight that adequate evaluation could not be made.

The aorta was obstructed for varying lengths of time ranging from five to fifteen minutes. Although resection of a segment of aorta and end-to-end anastomosis require from twenty to sixty minutes, it was felt that similar circulatory changes could be elicited by shorter periods of clamping. In two of the records the carotid arterial pressure showed a tendency to rise gradually over a period of minutes after the sharp initial rise. This was not a constant finding. In one record frequent extrasystoles were noted. This was the only time irregular heart rhythm was noted. The extrasystoles disappeared after the clamp was released, and a normal response to removal of the clamp was seen.

During all but one of the experiments the aortic clamp was released suddenly so that maximal effects would be produced. Immediately after release of the clamp there was a fall in the carotid arterial pressure to a level far below that existing before the clamp was applied. The fall was precipitous and was completed in a period of a few seconds. During that time the femoral arterial pressure rose to its normal relative position above the carotid arterial pressure. There was then a compensatory period during which the arterial pressure rose before finally falling to a stable level. Stabilization occurred within 90 to 180 seconds after release of the clamp. The blood pressure was usually lower during the stable period than the pressure before the clamp was applied.

There was a pronounced increase in the volume of the enclosed small intestinal segment above the volume existing before the clamp was applied. In the face of lowered arterial pressure this finding is indicative of splanchnic vasodilatation. Stasis of blood in areas distal to the clamp was demonstrated in one experiment by a rise of plasma lactic acid concentration and fall of plasma pH. Such an accumulation of metabolites is known to produce vasodilatation of small vessels. In these experiments the vasodilatation was not demonstrated by increased organ volume until after the arterial pressure in the visseral blood vessels was elevated by release of the clamp. There was then pooling of blood in the dilated vessels and an increase of organ volume. Such an effect is comparable to the reactive hyperemia seen in an extremity after removal of a tourniquet which has obstructed the blood supply for a period of time. The pooling of blood was accompanied uniformly by a fall of venous pressure in the superior vena cava indicating inadequate return of blood to the heart. Compensatory mechanisms had returned the venous pressure to adequate levels before the maximal splanchnic dilatation was seen in Fig. 1. The gradual return of splanchnic volume to preclamping levels was accompanied by a sustained rise of venous pressure above levels noted before the clamping.

Despite the fact that the aorta was clamped and unclamped two or three times in each animal, none of the animals expired during the period of stabilization after release of the clamp. One of the animals died about five minutes after the clamp was released and after arterial pressure and pulse rate had apparently stabilized. The changes in this animal are illustrated in Fig. 2. There was a progressive fall of venous pressure after release of the clamp. The low arterial pressure and rapid pulse indicated that the animal was in poor condition. The fall of venous pressure was not accompanied by accelerated pulse rate or fall of blood pressure during the time when the kymograph drum was running; such effects were observed for only a short period of time after the drum was stopped.

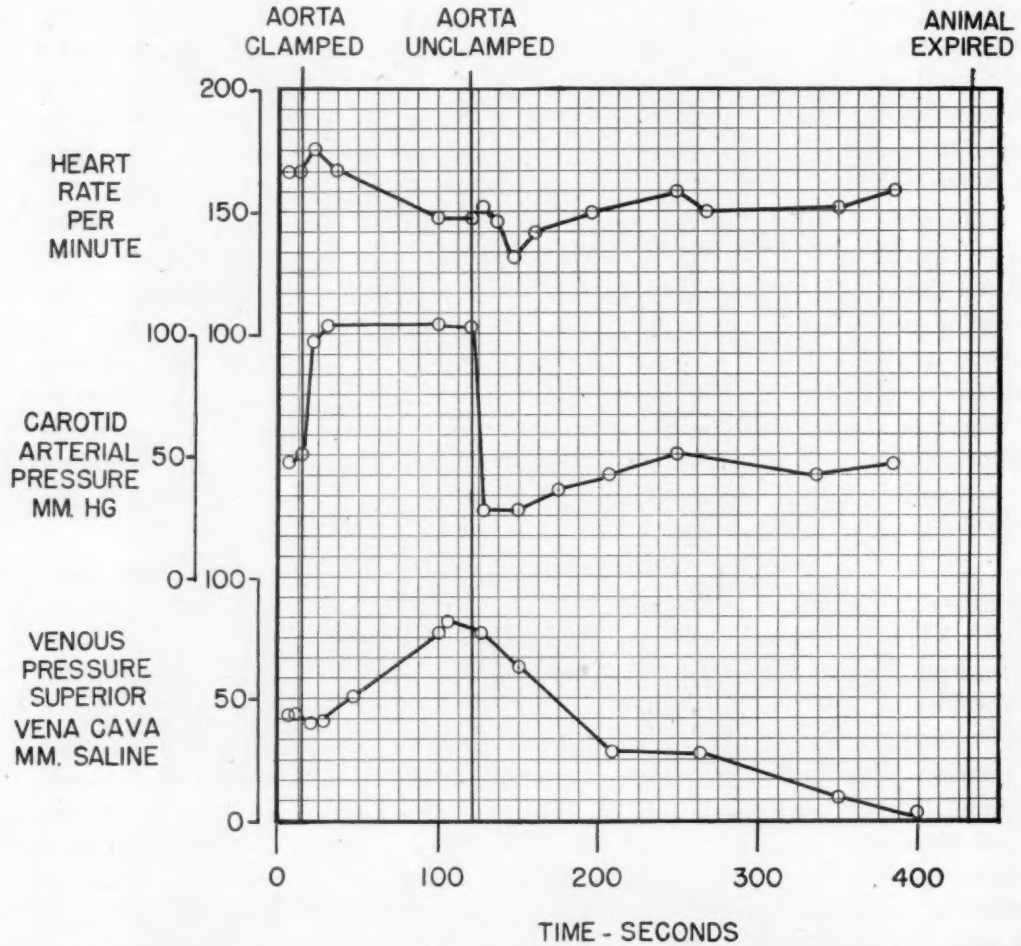

Fig. 2.—Circulatory changes prior to death in an animal under nembutal anesthesia showing the progressive fall of venous pressure in the superior vena cava.

In each of the animals after release of the clamp there was an increase in pulse rate. Again the alteration was less pronounced under nembutal anesthesia than under cyclopropane anesthesia. Typical effects of the two anesthetic agents are illustrated in Figs. 3 and 4. When nembutal was used the pressure

fell to lower levels during performance of the preliminary operations. This is attributed to the depressing effect of barbiturates on blood pressure associated with the trauma of removing the anterior chest wall. When the clamp was applied, the elevation of blood pressure was as prompt and as great with cyclopropane as with nembutal. In the animal treated with cyclopropane, there was a sharply reduced pulse rate, an expected response to elevated blood pressure. In the animal anesthetized with nembutal the pulse rate in this instance was actually accelerated for about one minute after application of the clamp.

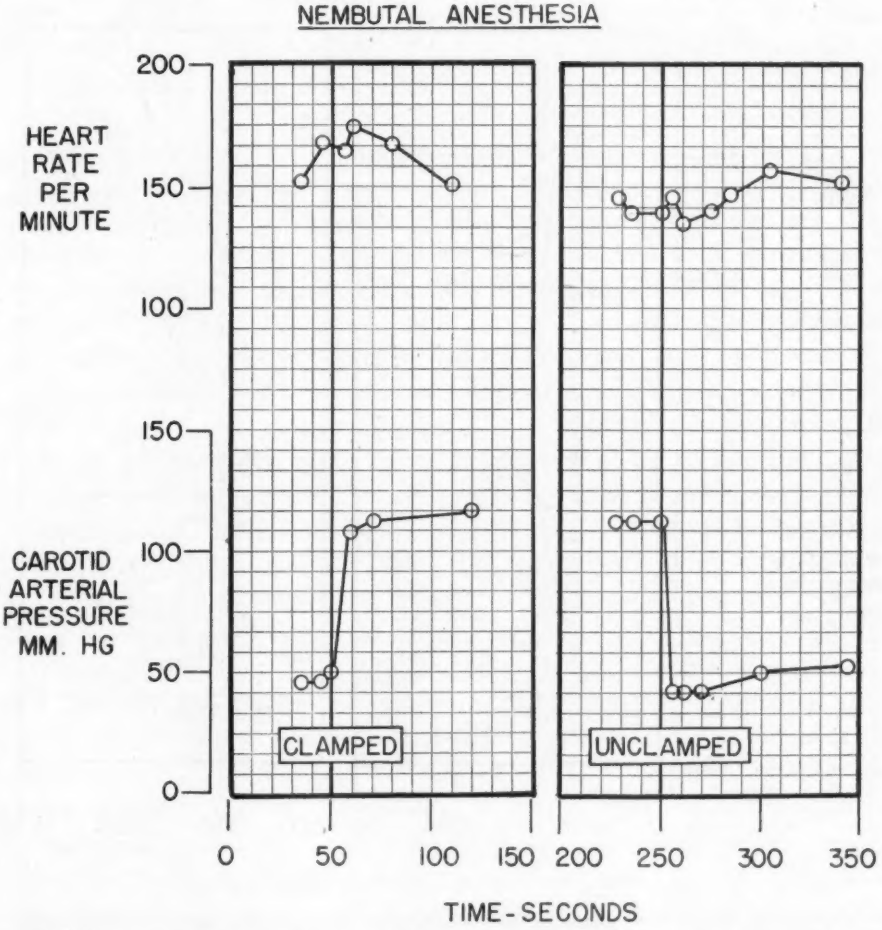

Fig. 3.—Response of arterial pressure and heart rate to clamping under nembutal anesthesia. Note the sluggish response of pulse rate to rapid fluctuations of arterial pressure.

There was then a gradual fall of heart rate during the remainder of the period of clamping. The bradycardia never assumed the proportions noted in the animal anesthetized with cyclopropane. Although the aorta was obstructed for a shorter period of time in the animal treated with nembutal, it was occluded for a length of time manyfold that during which maximal bradycardia was produced in the animal anesthetized with cyclopropane. Release of the clamp elicited a prompt fall of arterial pressure in both animals. The pulse rate under

cyclopropane rose from 104 to 192 in two minutes. The pulse of the animal treated with nembutal was only slightly accelerated. This may in part account for the stabilization of arterial pressure at a low level in the animal under nembutal at a time when the arterial pressure in the animal under cyclopropane was still rising. The usual anesthetic agents used in clinical thoracic procedures should elicit a response in pulse rate similar to that produced by cyclopropane.

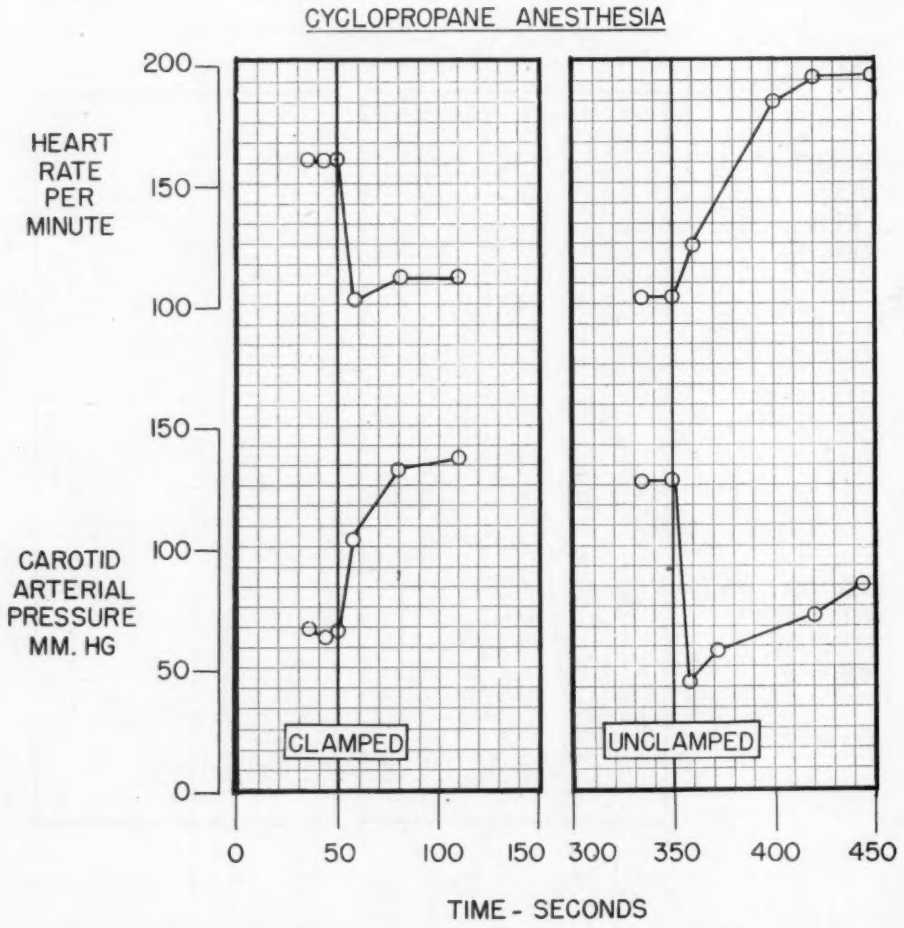

Fig. 4.—Response of arterial pressure and heart rate to clamping under cyclopropane anesthesia. Note the prompt response of heart rate to rapid fluctuations of arterial pressure.

In one experiment blood samples were withdrawn from the ascending aorta near the coronary ostia and analyzed for lactic acid and pH. The clamp was released after only eight minutes' obstruction. There was then a progressive rise of arterial lactic acid concentration over a period of three minutes after unclamping rising to a maximum of 150 mg. of lactic acid per 100 c.c. of plasma. Plasma pH fell during this period to a minimum of 7.2. Rapid buffering mechanisms were undoubtedly impaired by the mechanical regulation of gas exchange.

DISCUSSION

A pronounced increase of splanchnic volume is seen after the clamp is released despite the lowered arterial pressure. This would indicate appearance of reactive hyperemia in tissues distal to the site of aortic occlusion, and consequent pooling of blood in dilated vessels. The pooling of blood was accompanied by a reduction of venous return to the heart as indicated by a fall of pressure in the superior vena cava. The fall of venous pressure would suggest that the mechanism of failure is based upon inadequate filling of the heart chambers, that is, a hypodiastolic failure. Such a train of events was considered by Gross to follow release of the clamp. He introduced certain measures to insure that cardiac failure would not occur. The protection afforded by two of Gross' maneuvers, Trendelenburg position and slow release of the clamp, is illustrated in Fig. 5. Before the kymograph was started, the animal was placed in the Trendelenburg position by elevation of the foot of the animal board eighteen inches. Throughout the record venous pressure was elevated. Although the typical rise and fall of venous pressure was seen, adequate venous return to the heart was maintained at all times. Release of the aortic obstruction over a period of forty-five seconds produced a gradual reduction of the carotid arterial pressure without the precipitous fall and compensatory rise seen when the clamp was released suddenly. Gross released the clamps even more slowly over a period of minutes. The splanchnic volume showed no increase above preclamping levels but gradually returned to approximately the preclamping level over a period of five minutes. Such an effect is probably due to a "washing out" of metabolites and improved oxygenation of anoxic areas with subsequent improvement of vasomotor tonus before the full force of arterial pressure is transmitted into the splanchnic vascular bed.

It is uncertain whether the acceleration of pulse noted in the animal treated with cyclopropane is a desirable adjustment to the fall of arterial pressure. The demand for increased cardiac output cannot be met by acceleration of pulse rate unless venous return is maintained at the same time. In the face of falling venous pressure cardiac acceleration can conceivably result in less economical utilization of energy by heart muscle due to the reduction of stroke volume.

In certain respects the conditions of these experiments differ from those prevailing in the human patient with coarctation of the aorta. Long-standing coarctation of the aorta is associated with the development of extensive collateral circulation around the site of constriction. Consequently, there is less derangement of circulation distal to the clamps when a coarctation is isolated than when a normal aorta is clamped. That the circulation is not adequate in normal dogs is shown by the high incidence of hind limb paralysis noted by Gross and Hufnagel after they had divided and re-anastomosed the aorta. Deficiency of collateral circulation is further enhanced in the present experiments by ligation of the internal mammary arteries and upper intercostal arteries. Because of these conditions it is unlikely that changes as great as these would occur in the human patient, but it might be suspected that changes of a similar nature would be observed.

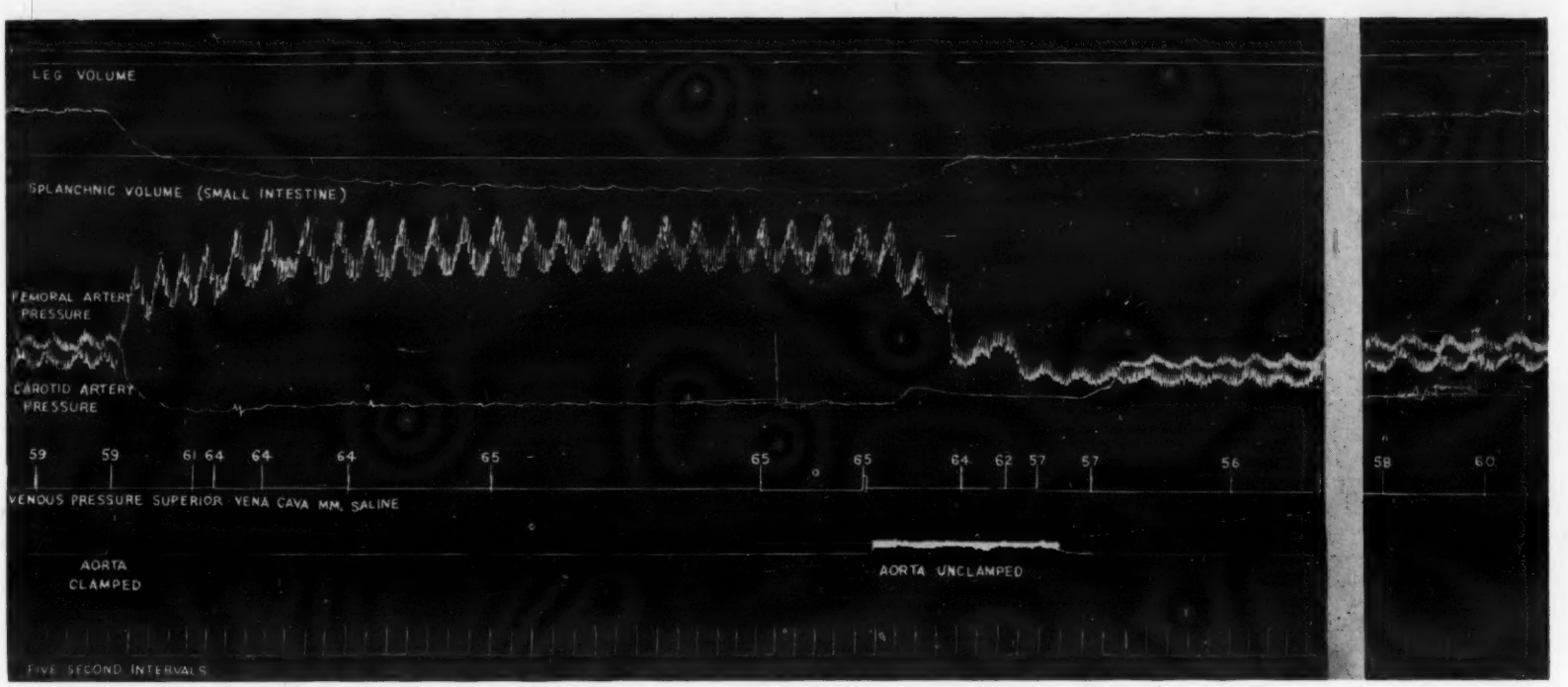
LEG VOLUME
SPLANCHNIC VOLUME (SMALL INTESTINE)
FEMORAL ARTERY PRESSURE
CAROTID ARTERY PRESSURE
59 59 61 64 64 64 65 65 65 64 62 57 57 56 58 60
VENOUS PRESSURE SUPERIOR VENA CAVA MM. SALINE
AORTA CLAMPED
AORTA UNCLAMPED
FIVE SECOND INTERVALS

Fig. 5.—Response to slow unclamping of the aorta in a dog under nembutal anesthesia in the Trendelenburg position. The first break in the record represents an interval of three minutes.

Because of the mobile mediastinum the opening of one pleural space creates a bilateral open pneumothorax in the dog. Respiratory exchange must then be maintained by some device for insufflation of air or oxygen under positive pressure into the lungs. Similar conditions would prevail in the human being only where a bilateral open pneumothorax was created inadvertently by the surgeon or where a "controlled" type of bag breathing was instituted by the anesthetist. Under these conditions rapid variations in carbon dioxide content or pH would not be as rapidly compensated by altered ventilation since the patient would be separated from the control of his respiratory center.

SUMMARY

1. The thoracic aorta was obstructed in a series of dogs and the circulatory changes were studied by recording of carotid arterial pressure femoral arterial pressure, pressure in the superior vena cava, splanchnic volume (small intestine), and leg volume.

2. Following obstruction of the thoracic aorta there is a rise in the pressure in the carotid artery and in the vena cava. After the clamp is removed there is a fall of carotid arterial pressure and a fall of caval pressure accompanied by a pronounced increase of splanchnic volume. The increased organ volume is attributed to pooling of blood due to vasodilatation in anoxic tissues distal to the site of aortic obstruction. The fall of venous pressure indicates inadequate return of blood to the heart.

3. Despite the conditions in these experiments which would be expected to impose a maximal strain upon the heart, death occurred only once immediately after the clamp was released. The death was preceded by a gradual progressive fall of venous pressure.

4. These findings support the suggestions of Gross that the heart failure he had observed in a human patient after surgical excision of a coarcted segment of aorta was caused by inadequate venous return to the heart. The supportive measures he introduced for assuring that venous return is maintained are shown to be well suited for that purpose.

I wish to thank Dr. William B. Youmans and Dr. William S. Conklin for many helpful suggestions during the development of this paper.

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THE SUBCUTANEOUS INGUINAL RING: A CLINICAL STUDY

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ROUTINE physical examination at an army separation center has served to emphasize certain points of confusion regarding examination of the inguinal region. Numerous textbooks[1-7] state that the normal subcutaneous ring should not admit the tip of the index finger. Nevertheless, on routine palpation many apparently healthy young men were found to have large subcutaneous rings. Considerable disagreement arose as to the significance of this finding. There was no clear-cut conception of the range of normal variation in the size of the external rings. Survey of the recent literature did not provide a solution to this problem. As a result, this study was undertaken in order to determine the range of sizes of the subcutaneous rings in large numbers of healthy young men.

MATERIAL AND METHODS

Three thousand one hundred ninety-nine (3,199) soldiers between the ages of 18 and 36 years, who were being separated from the service, formed the basis of this study. I examined these men for hernia as part of the final type physical examination. After considerable preliminary study the following examining routine, similar to that described by Carp,[8] was developed.

The patient, stripped, stood erect before the examiner. Routine palpation of the scrotal contents was performed. The right index finger was used to invaginate the scrotum until the volar surface of the finger tip rode over the patient's left pubic tubercle. The finger then slid laterally for about 0.5 to 1.5 cm. at which point it suddenly dipped into a sharply delineated aperture comprising the subcutaneous inguinal ring. The identity of this structure was always confirmed by following the course of the spermatic cord into the inguinal canal.

Patency of the ring was tested by an attempt to insert the finger into the inguinal canal. Since cases have been reported[1] of hernias which were traumatically induced by such a procedure, it was carried out with some caution. The margins of the ring were explored with the finger tip, and the length of the longest diameter was recorded. The width of my finger tip, measuring 1.3 cm., served as a standard for estimating the diameter of each ring.

Following this step the patient was told to "strain down as if you were trying to move your bowels!" This action, properly executed, served effectively to increase intra-abdominal tension and to force occult hernias through the in-

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guinal rings. In addition, the patients were instructed to cough while the examining finger attempted to elicit a hernial cough impulse at the external ring. Men in whom hernias were discovered during this examination were thereupon omitted from further consideration in this series.

In thirteen men various difficulties were encountered which were serious enough to warrant rejection of the findings. In ten of these men adequate examination was prevented by lack of cooperation or the tickling reflex, or both, while in three cases the subcutaneous rings could not be satisfactorily located by palpation despite adequate cooperation.

A total of 221 men were excluded from this series for the reasons shown in Table I.

TABLE I

Previous hernioplastic operations	122
Inguinal hernias discovered	66
Cryptorchidism, or history of operation for this condition	19
Lack of cooperation and/or tickling reflex	10
Subcutaneous rings not satisfactorily located	3
Shrapnel wound of the inguinal region requiring extensive reparative surgery	1
Total	221

The terms "subcutaneous inguinal ring" and "external ring," are used synonymously in this report, as are the terms "abdominal inguinal ring" and "internal ring."

OBSERVATIONS

Of the 5,956 subcutaneous inguinal rings in the 2,978 men remaining after rejection of those listed in Table I, 78.1 per cent were large enough to admit the index finger without force. The detailed findings are summarized in Table II.

TABLE II. DISTRIBUTION OF THE SIZES OF 5,956 SUBCUTANEOUS INGUINAL RINGS FOUND IN 2,978 HEALTHY YOUNG MEN

	DIAMETER OF SUBCUTANEOUS RINGS IN CENTIMETERS:				
	0-0.9	1.0-1.3	1.4-1.9	2.0-2.9	3.0-5.0
Symmetrical	506	362	2,544	900	196
Asymmetrical*	163	277	597	334	77
Total	669	639	3,141	1,234	273
Per cent distribution	11.2%	10.7%	52.8%	20.7%	4.6%

*Of the 724 men in this group, 416 or 57.5 per cent had the larger subcutaneous ring on the *left* side.

Of the sixty unilateral inguinal hernias discovered in this study, thirty-five or 58.3 per cent occurred on the right side. This tendency of hernias to occur on the right side has long been recognized. It is usually attributed to the fact that the right testis descends later in the human fetus than does the left.[1]

On the other hand, 57.5 per cent of the 724 men who had inguinal rings of unequal size had the larger ring on the left side. The reason for this situation is not clear. Perhaps the more frequent occurrence of varicocele on the left may offer a partial explanation.

DISCUSSION

Gray's Anatomy[9] gives the measurements of the subcutaneous ring in cadavers as 2.5 by 1.25 cm. However, according to various authorities, the dimensions of this structure, as determined by clinical examination, are as follows:

> "It (the annulus inguinalis subcutaneus) should merely admit the tip of the little finger; if more than this is possible, the ring is not of normal dimensions." (Iason,[1] p. 377.)
>
> "The normal external ring will seldom admit the tip of the little finger and it is impossible to palpate the inguinal canal or the internal ring." (Watson,[2] p. 118.)
>
> "Ordinarily this (external abdominal) ring will not admit the finger tip, although about 3% of male adults have a larger or relaxed ring, which predisposes to the later occurrence of direct herniae." (Erdman in Christopher,[3] p. 1369.)
>
> "Normally it is barely large enough to admit the tip of the index finger. . ." (Cole and Elman,[4] p. 786.)
>
> "In a healthy man the external ring should admit the tip of the little finger, but not the index finger. If the end of the index finger can be entered into the ring that aperture is dilated, and even if there is no hernia in the canal, in the future a hernia will probably descend." (DaCosta,[5] p. 1050.)
>
> "The ring when normal in size cannot be entered (by the tip of the index finger) . . ." (Callander,[6] p. 289.)
>
> "The average normal external abdominal ring will not completely admit the tip of the fifth finger." (Orr,[7] p. 431.)

Several other standard surgical reference books[10-12] do not give any measurements for the normal subcutaneous ring.

Our results (Table II) are not consistent with these quoted statements, since 78.1 per cent of the healthy young men in this select series had subcutaneous rings large enough to admit the index finger. This would tend to show that the range of variation among normal external rings is rather wide. Also, the average ring is probably significantly larger than was heretofore believed.

The question then arises as to whether a large subcutaneous ring may predispose to the future development of inguinal hernia, especially of the direct type. This is the contention of Erdman in Christopher[3] and DaCosta[5] as quoted previously. On the other hand, considerable evidence has accumulated[13-16] which points to weakness of the transversalis fascia as the major factor in the pathogenesis of direct hernia. In almost all of our cases the transversalis fascia forming the posterior wall of the inguinal canal in the region of Hesselbach's triangle was found to be tense and unyielding when the patient was subjected to the straining test. This was true even among the men who had subcutaneous rings 4.0 and 5.0 cm. in length.

In the case of indirect hernia it is even less likely that enlargement of the external ring is a predisposing factor. Here the essential etiological mechanism

is congenital patency of the processus vaginalis[17, 18] and the most important line of defense is a competent internal ring.[19] Once an incomplete hernia has entered the inguinal canal, it is unlikely that a small subcutaneous ring can do more than delay the eventual descent of a complete indirect hernia.

Further evidence regarding the significance of a large external ring can be adduced from the follow-up studies of Colcord and of Gardner. Colcord[20] found enlarged or "open" external rings in 784 out of 9,000 men whose physical condition was checked frequently during their periods of employment. The incidence of hernias in the group of men with "open" rings was not significantly greater than in the control group. Gardner[21] found that 3,413 (or 13.6 per cent) of a group of 24,934 civil service pre-employment physical examinations revealed relaxation of the external rings. In the subsequent fifteen-year period ten men who had had relaxed rings (an incidence of 0.322 per cent) and forty-two men of the control group (0.176 per cent) developed hernias. Although this difference in incidence rates may appear to be statistically significant, it is certainly not impressive. Much more striking is the fact that of 3,413 men with relaxed rings who were admitted to full industrial employment in a navy yard, only ten were known to have developed hernias over a period of fifteen years.

Considering these facts, it would seem reasonable to conclude that there is at this time no convincing evidence that a large subcutaneous ring either is in itself an abnormal finding or that it predisposes to the future development of herniation. Nor should it be thought to disqualify men from industrial employment.

An attempt was made during this study to correlate the size of the subcutaneous rings with the height and with the weight of the patient, but no correlation could be demonstrated. No attempt was made at correlation with the length of the inguinal ligament, although this might prove interesting in view of the work of Harris and White[22] and Hillenbrand,[23] which indicates that men with long inguinal ligaments are more likely to develop weakness and herniation of the direct type than are men with short inguinal ligaments.

SUMMARY AND CONCLUSIONS

1. In a series of 2,978 healthy young men, 78.1 per cent of the subcutaneous inguinal rings were large enough to admit the examiner's index finger.

2. Of the 724 men whose subcutaneous rings were not bilaterally equal in size, 57.5 per cent were larger on the left side.

3. Enlargement of the subcutaneous ring alone should not be considered to be abnormal, nor is there any conclusive evidence that it constitutes a predisposing factor in the pathogenesis of inguinal hernia.

4. There was no correlation between the size of the subcutaneous ring and either height or weight.

The author wishes to express his appreciation for the advice and criticism of Dr. Henry N. Harkins, Baltimore, Md., and Dr. Charles G. Mixter, Boston, Mass.

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AMBULATORY TREATMENT OF HALLUX VALGUS

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PROLONGED rigid splinting and restriction of walking activity for periods of from two to six weeks have constituted the routine of most orthopedic surgeons after operations for correction of hallux valgus. As a result of this prolonged immobilization without the functional stimulus of weight-bearing and walking, some permanent loss of motion in the metatarsal phalangeal joint has followed many of the operations. Hallux rigidus or hallux varus, which occasionally resulted, produced severe disability.

In addition to these complications, which may be relatively infrequent in the hands of experienced orthopedic surgeons, there is always greater cost and hence an economic objection to prolonged hospitalization made necessary by the usual procedure of rigid splinting and non-weight-bearing for a period of several weeks.

During the years 1940 and 1941, one of us (E. L. C.) conducted an outpatient clinic in the Central Free Dispensary of Rush Medical College. The patients in this clinic were mostly adults and a considerable proportion of them were 45 years of age or older. A common complaint of patients coming to the clinic was that of painful feet due to bunions. It was impossible to obtain hospital beds for service patients of this type. We determined to attempt to carry out surgical procedures for excision of the bunions and correction of the hallux valgus in the operating room of this outpatient clinic.

The operations were carried out under local anesthesia. The block of the metatarsal phalangeal region was started at midfoot and a tourniquet applied around the foot at that level. The surgical techniques used included the McBride, the Mayo, and the Silver operations with various modifications. The sesamoid bones were removed whenever they were found to be hypertrophied or their articular surfaces degenerated. Débridement of the joint was carried out when indicated. No rigid splint of any kind was used. *In each instance the toe was held in a position of varus by corrective bandaging* (Fig 1). The blood which subsequently stained the dressing dried to further reinforce the bandage. Patients were permitted to walk from the operating room without assistance (Fig. 2). Absence of pain because of the novocain anesthesia made it comparatively simple to persuade them to do this. Most of them had to go home by streetcar and some of them traveled long distances. The dressing was inspected the following week, but was not changed for two weeks after the operation.

A total of twenty-four patients were subjected to one or more operations for hallux valgus and then permitted to go home immediately by whatever

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transportation they could obtain. There were no complications. The results which were obtained were definitely better than those which had been observed in our patients whose care had included two to three weeks of hospitalization with complete immobilization. These patients suffered minimal pain and all of them returned to the clinic walking surprisingly well and with an excellent range of motion in the metatarsal phalangeal joint (Figs. 3 and 4).

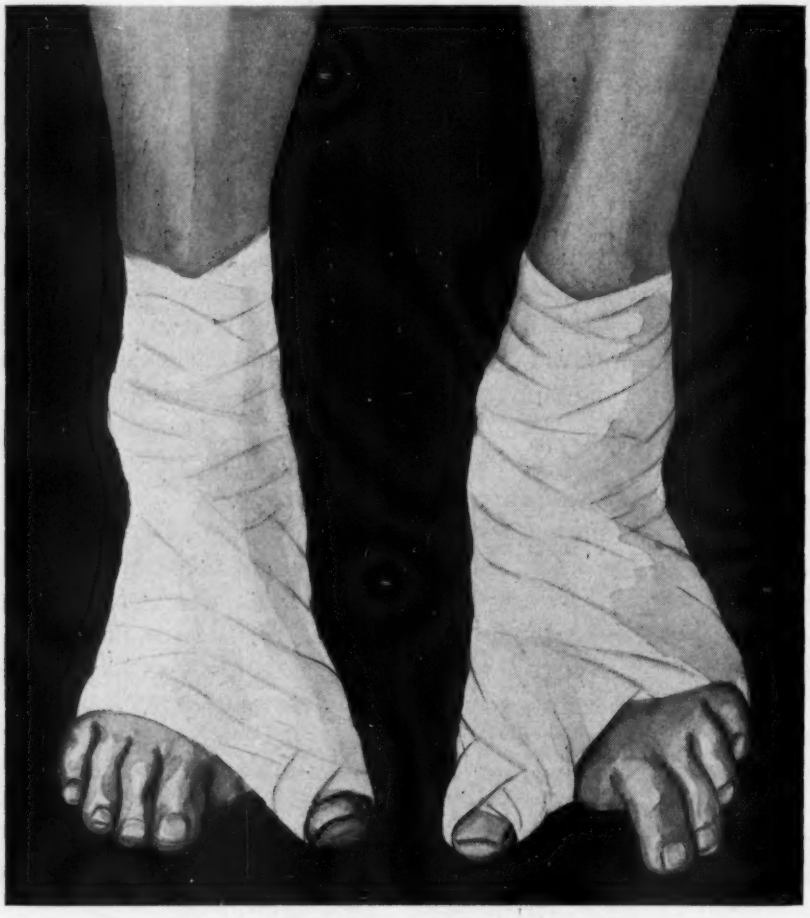

Fig. 1.—Artist's sketch of bandaged splinting made immediately after bilateral bunionectomies under local anesthesia, with the patient standing.

One patient, a chronic alcoholic, disappeared after the operation and did not return for the postoperative appointments. When he was finally located, more than a month after operation, he still had the original dressing. Although the bandages were extremely dirty and ragged, the wound was found to be completely healed. There was no swelling and the range of motion and strength in the movement of the hallux was approximately normal.

Encouraged by these results, our program of care for private patients was changed to conform. Since 1941, we have performed twenty-six operations on seventeen hospitalized patients for hallux valgus and bunions. A general anesthetic was used in six cases because the patient refused to permit the use of

local or because other surgical procedures were to be carried out simultaneously. In eleven cases 1 per cent novocain was used as a local anesthetic. The patients who were operated upon under local anesthesia were encouraged to walk about their rooms immediately after the operation and were given bathroom privileges. Because of the persisting anesthesia, they experienced no pain. On the second and third day these patients did complain of some pain, but not sufficient to prevent them from bearing weight and walking.

Fig. 2.—Photograph following bandaging of great toe to demonstrate how well the toe may be held in a varus position without any type of rigid splint. Overcorrection by means of bandaging requires many layers of bandage, preferably two complete gauze bandages being used. This is the most significant departure from the standard treatment of bunions and makes possible immediate ambulation.

The patients for whom this procedure was used included a range of ages from 23 to 75 years. The occupations were those in which at least an average amount of walking was necessary. These patients were discharged as recovered four to eight weeks following surgery. There have been no complications or

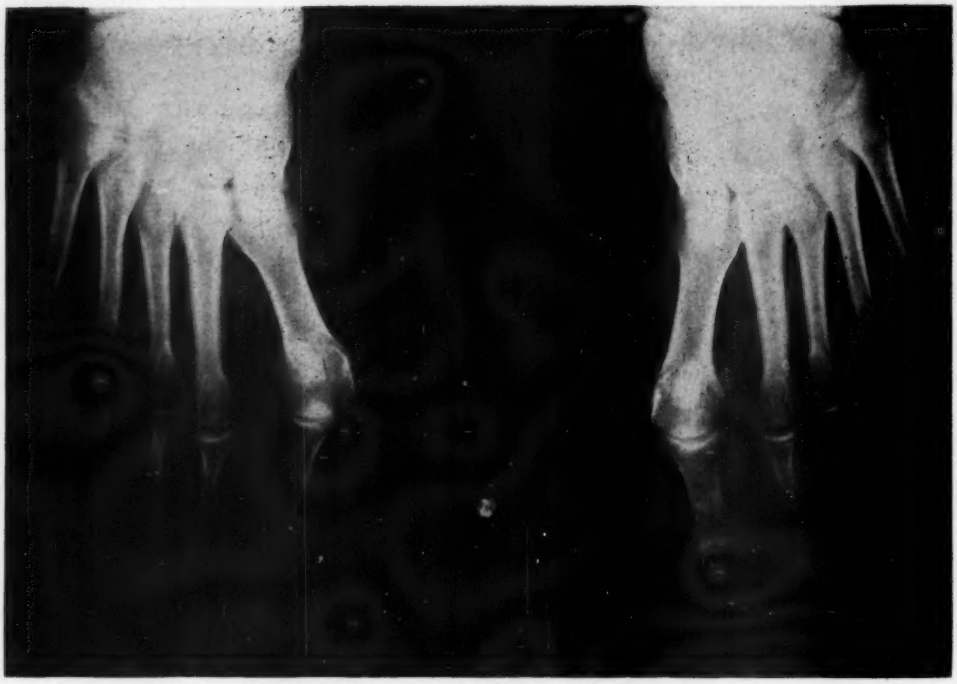

Fig. 3.—These preoperative x-rays show the hallux valgus deformity and exostoses of the first metatarsal bones.

Fig. 4.—Same case as Fig. 3, following operation. Correction of the deformity is maintained by bandaging.

unfortunate sequelae and we are enthusiastic about this method of ambulatory tratement without rigid splinting.

The plan of postoperative care may be summarized as follows:

1. The hallux should be splinted by means of corrective bandaging, without rigid fixation, following operation. Two two-inch gauze bandages should be used for each foot. *Multiple layers of bandage* are essential if correction of the hallux valgus is to be maintained while ambulation is permitted.

2. Walking with full weight-bearing is begun immediately when a local anesthetic is used, and on the day following an operation carried out under general anesthesia.

3. The patient may be discharged from the hospital two to four days after operation.

4. The original dressing should be changed and the stitches removed fourteen days after operation.

5. The functional splinting by corrective bandaging should be continued for an additional period of two weeks.

6. Patients may be encouraged to resume their normal activities at the time that the bandaging is discontinued.

7. After bandage splinting is discontinued, the foot should be soaked in warm, slightly soapy water for twenty minutes each day. While in the warm water the toe should be actively exercised.

8. Low heel, soft leather oxford shoes with a stiff shank, straight inside last, and metatarsal pads should be worn for at least three months.

The advantages of functional splinting without rigid fixation of the hallux after operation for the cure of hallux valgus include:

1. Immediate activity with walking. Hallux valgus is corrected, while flexion and extension are permitted.

2. Motion in the metatarsal phalangeal joint is preserved by early function.

3. The hospital stay is greatly shortened.

4. Circulatory changes in the foot, which are common sequelae of prolonged immobilization and inactivity, are minimal.

5. Time lost from work is reduced.

AN IMPROVED METHOD FOR PRODUCING EXPERIMENTAL PERITONITIS OF INTESTINAL ORIGIN IN DOGS

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EXPERIMENTAL peritonitis in dogs is not identical with peritonitis in human patients, but it appears to be sufficiently comparable to serve as a useful medium for bacteriologic and physiologic studies, and as an aid in the evaluation of therapeutic agents and methods.

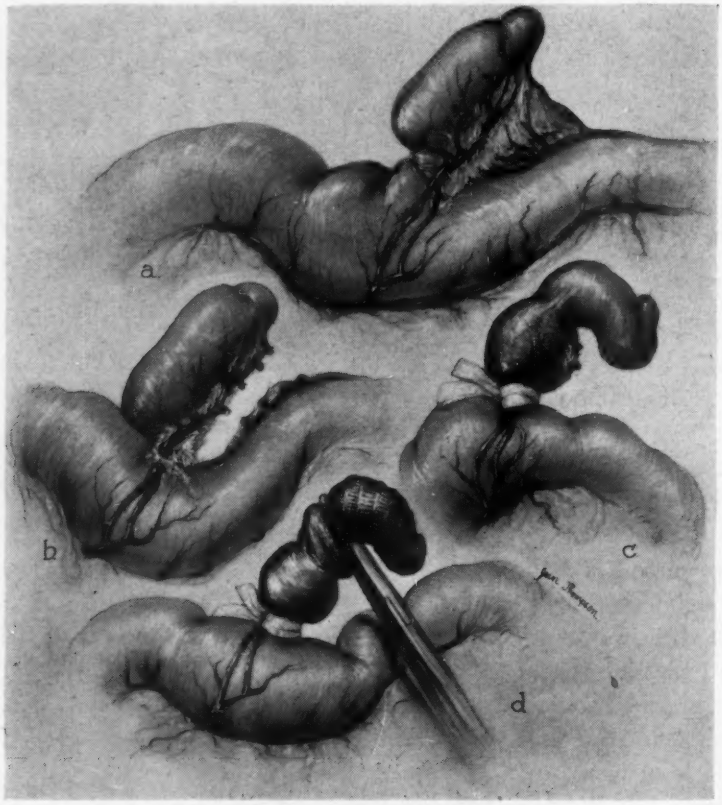

Fig. 1.—Technique for producing experimental peritonitis of appendical origin. *a*, Anatomic relations of the appendix often present in the dog; *b*, vascular supply of the appendix is ligated; *c*, the base of the appendix is tied with a cotton tape; *d*, the wall of the appendix is crushed uniformly with a clamp.

A procedure that consists of dividing the blood supply and ligating the base of the appendix, followed by a dose of 54 c.c. of castor oil, has been described[1, 2] as a suitable method of producing experimental peritonitis in the dog. However, following this procedure the appendix often becomes walled off by omentum and spleen and the infection remains localized without producing a peritonitis.

In an attempt to improve this method a series of dogs was subjected to the following procedure: The vascular supply of the appendix was divided and

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ligated; a flat cotton tape ¼ inch in width was tied firmly about the base of the appendix; the entire wall of the appendix was crushed by repeated clamping with a Kocher hemostatic clamp; the omentum was excised and the spleen removed; the animal was given 50 c.c. of castor oil by gavage. This procedure uniformly produced a fulminating, diffuse peritonitis in all of a series of fifty-six dogs. The average period of survival in untreated animals was thirty-nine hours.

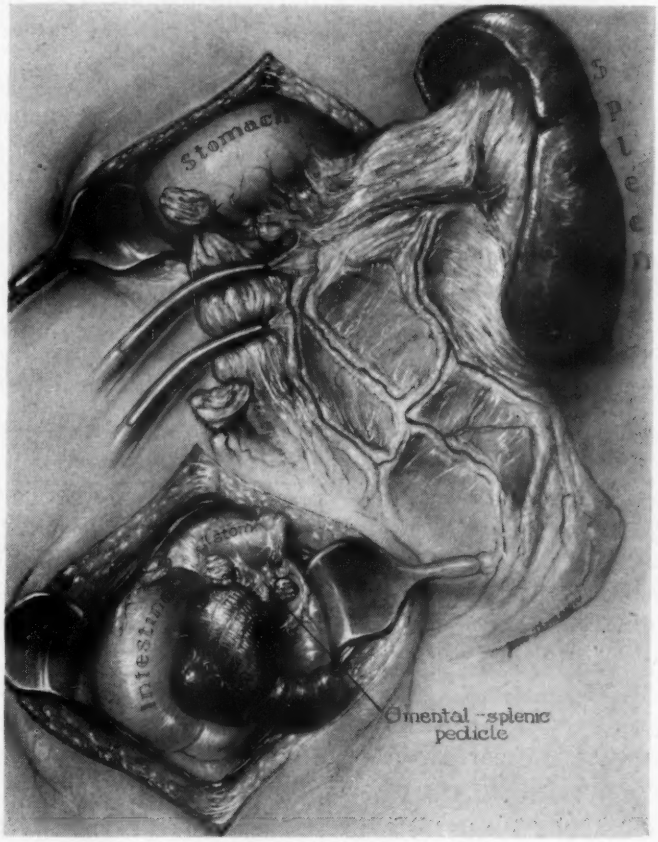

Fig. 2.—Final step in technique for producing experimental peritonitis of appendical origin in dogs; removal of omentum and spleen. Note crushed appendix with base ligated and vascular supply divided.

SUMMARY

A fatal, fulminating diffuse peritonitis of appendical origin may be uniformly produced in dogs by a series of procedures including ligation of the appendical vessels, placing a tape ligature about the base of the appendix, crushing the wall of the appendix, excising the spleen and omentum, and administering castor oil postoperatively.

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EXPERIMENTAL PRODUCTION OF ULCERS IN CLOSED GASTRIC POUCHES IN DOGS

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A WEALTH of evidence attests the important role of acid pepsin in the production of experimental peptic ulceration and in the genesis of human gastroduodenal ulcerative disease. Although this evidence indicates that acid pepsin is a sine qua non for the existence of peptic ulcer, the cooperation of other factors is evident in both experimental and human peptic ulcers. For example, the continuous administration of histamine induces ulcers, but the relative importance of acid production and the angiotoxic action of histamine in the genesis of these ulcers has not been elucidated.

One of the most important factors conditioning the effect of acid pepsin is the gradient of susceptibility manifested by the gastrointestinal mucosa. It is well known that the resistance of intestinal mucosa to gastric juice decreases progressively from the stomach to the colon. Exposure of the mucosa from the duodenum, jejunum, ileum, or colon to relatively pure gastric juice usually results in ulcers. This may be accomplished by placing intestinal transplants in the stomach and preventing duodenal regurgitation, as in the method of Matthews and Dragstedt,[1] by surgical duodenal drainage using the Mann-Williamson technique or by creating an experimental Meckel's diverticulum as in the experiments of Matthews and Dragstedt.[1] These procedures rarely result in gastric ulcers, and, moreover, the mucosa of isolated gastric pouches of most types, although in contact with pure gastric juice, seldom shows spontaneous ulceration. Dragstedt[3] reported the formation of ulcers in total gastric pouches in which vagus innervation was preserved. Ivy has not noted ulcers in total gastric pouches either with or without vagus innervation. In Dragstedt's experiments a metal cannula was used and this may have served as a mechanical traumatic factor.

Hay, Varco, Code, and Wangensteen[4] demonstrated that injections of histamine in beeswax produce duodenal and occasionally gastric ulcers in a large percentage of animals. These ulcers were attributed to the effect of prolonged maximal secretion of hydrochloric acid on the gastric and duodenal mucosa.

Those experimental procedures which lead to a predominance of gastric rather than duodenal ulcers, of which the principal examples are cinchophen and caffeine, cause, in addition to stimulation of gastric secretion, vascular and inflammatory changes in the gastric mucosa.[8, 9] Therefore, it must be considered questionable whether prolonged exposure of the gastric mucosa to acid pepsin is in itself sufficient to elicit ulcer formation.

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The following experiment was undertaken in an attempt to elucidate further the role acid pepsin plays in ulcer production and to ascertain if continuous exposure of gastric mucosa to normal gastric juice would result in ulcer formation.

METHOD

Healthy mongrel dogs, weighing from 25 to 35 pounds, were used and all operations were performed under ether and morphine anesthesia with aseptic technique. A portion of the greater curvature of the stomach, comprising one-third to one-half of the fundus of the stomach, was resected in the first group of five dogs. This was done as in the Heidenhain technique,[5] however, the resected segment was completely sutured into a closed pouch. Closure of both the stomach and the pouch was done by the open method using a separate continuous row of mucosal and serosal Lembert sutures. A clamp was used for the remaining gastric portion in all cases, however, in only three out of five was a clamp placed on the pouch.

A second group consisted of eight dogs. A two-stage procedure was employed, the first being the construction of the usual Heidenhain pouch. After from nine to eighteen days, the dog was reoperated upon, and the stoma of the Heidenhain pouch was tightly sutured in two layers, producing a closed gastric pouch.

A third group consisted of six dogs. Primary closure was established as in the first group, following which an avascular area of the middle or inferior end of the pouch was attached to the parietal peritoneum underlying the second left nipple, which was used as a point of localization. Twenty-four hours postoperatively a 15 gauge needle was inserted through the abdominal wall into the pouch, a pressure determination was made with a water manometer, and gastric juice collected to relieve pressure and also for titration. Thereafter readings were made every twelve or twenty-four hours depending on the volume collected and pressure within the pouch.

RESULTS

Group I (see Table I).—All five dogs in the first group died in two to five days due to acute ulcer formation with perforation and peritonitis. The site of ulceration was 0.6 cm. from the suture line in three dogs, and 3 cm. from the suture line in one dog.

TABLE I. HEIDENHAIN POUCH TECHNIQUE, PRIMARY CLOSURE

DOG NO.	PROCEDURE	RESULTS
2	Heidenhain pouch closure without stoma	Died 2 days postoperatively; perforation of pouch with peritonitis
3	Heidenhain pouch closure without stoma	Died after 3 days; 1 cm. ulcer of pouch with perforation 0.6 cm. from suture line, peritonitis
4	Heidenhain pouch closure without stoma	Died after 5 days; 1 cm. acute ulcer with perforation in central portion of pouch 3 cm. from suture line, peritonitis
5	Heidenhain pouch closure without stoma; no clamps applied to pouch	Died after 3 days; perforation of pouch 0.6 cm. from suture line, peritonitis
6	Heidenhain pouch closure without stoma, no clamps applied to pouch	Died after 2 days; perforation of pouch 0.6 cm. from suture line, peritonitis

Group II (see Table II).—Four of the eight dogs in the second group died of acute ulcers with peritonitis in three to eight days following closure of the stoma. Three dogs died of intercurrent causes without ulcer. One dog was sacrificed twenty days after closure of the stoma. The pouch was greatly distended, but showed no pathological change.

TABLE II. HEIDENHAIN POUCH, SECONDARY CLOSURE

DOG NO.	PROCEDURE	RESULTS
7	Heidenhain pouch stoma closed after 14 days	Died 4 days after closure of stoma; leakage of stomal closure, peritonitis
8	Heidenhain pouch stoma closed after 16 days	Died 3 days after closure of stoma; pouch intact and filled with brown fluid, several small mucosal erosions
9	Heidenhain pouch stoma closed after 14 days	Sacrificed 20 days after closure of stoma; evidence of much weight loss, pouch intact, greatly distended, measuring 16 by 7 cm.; mucosa thin and pale, no erosions, filled with thick milky fluid, black discoloration of omentum
10	Heidenhain pouch stoma closed after 18 days	Died 13 days after closure of stoma; pouch and stomach showed no pathologic change
12	Heidenhain pouch stoma closed after 13 days	Died 3 days after closure of stoma; small perforation in middle of pouch wall not near suture lines, hemorrhagic fluid in peritoneal cavity
13	Heidenhain pouch stoma closed after 13 days	Died 8 days after closure of stoma; acute ulcer superior end of pouch 5 cm. in diameter and 7 cm. from suture line, small perforation of ulcer with acute peritonitis; free fluid in peritoneal cavity
16	Heidenhain pouch stoma closed after 9 days	Died 5 days after closure of stoma, chocolate colored fluid in peritoneal cavity; peritonitis, plastic exudate, extensive adhesions, paralytic ileus, pouch contracted down contained no blood, 1 cm. perforation of pouch not near suture line
17	Heidenhain pouch stoma closed after 13 days	Died 8 days after closure of stoma; 0.8 cm. perforation at superior end of pouch not near suture line, abscess cavity extending from perforation filled with dark brown fluid and surrounded by omentum, spleen and loops of small intestine

Group III (see Table III).—Four of six dogs in the third group died in seven to twelve days of acute ulceration of the pouch with perforation and acute peritonitis. Two of the dogs died in thirteen and fourteen days from extraneous causes. The average amount of gastric juice withdrawn for a twenty-four hour period, the free-acid range and average, and the pressure range and average for each dog are noted in Table III.

All the animals with an average free-acid concentration of over 40 meq. per L. had acute ulcer formation with perforation. The two dogs which died of complications showed average free acid of 14 meq. per L. and 36 meq. per L.

DISCUSSION

The fate of closed gastric pouches has not been studied previously.

Perforation of the gastric pouch in Group I was questionably due to trauma caused either by the pressure of the clamp or by the underlying suture, for

TABLE III. HEIDENHAIN POUCH, PRESSURE RELIEVED BY ASPIRATION

DOG NO.	PROCEDURE	FREE-ACID CONCENTRATION		PRESSURE CM. H_2O		AVE. AMT. WITHDRAWN PER 24 HR. (C.C.)	REMARKS	RESULTS
		RANGE (MEQ. PER L.)	AVE. (MEQ. PER L.)	RANGE	AVE.			
24	Closed Heidenhain pouch attached to abdominal wall for aspiration	12-81	59	10-50	29	89	Pressure 10 cm. H_2O and 70 c.c. withdrawn 24 hr. before death; aspiration every 24 hr.	Died after 9 days; acute generalized peritonitis, 1 cm. perforation of pouch on superior lateral aspect of pouch 2.5 cm., 1 to 5 mm. shallow mucosal ulcers surrounding perforated ulcer
25	Closed Heidenhain pouch attached to abdominal wall for aspiration	44-117	76	0-68	24	149	Pressure 9 cm. H_2O and 80 c.c. withdrawn 24 hr. before death; aspiration every 24 hr.	Died after 12 days; acute generalized peritonitis due to 0.8 cm. perforation of pouch at approximately same site as No. 24, not near puncture site or suture line
26	Closed Heidenhain pouch attached to abdominal wall for aspiration	0-102	49	6-8	7	101	Pressure 7 cm. H_2O 190 c.c. withdrawn 24 hr. before death; aspiration every 24 hr.	Died after 7 days; acute ulcer of pouch with perforation and acute peritonitis, perforation not near suture line or puncture site, in superior end of pouch
29	Closed Heidenhain pouch attached to abdominal wall for aspiration	0-59	14	0-20	2	33	Aspirated every 12 hr.; did not eat well last 5 days	Died after 13 days; pouch and stomach normal
30	Closed Heidenhain pouch attached to abdominal wall for aspiration	0-76	36	0-20	8	111	Aspirated every 12 hours; did not eat well last 5 days	Died after 14 days; pouch and stomach normal
31	Closed Heidenhain pouch attached to abdominal wall for aspiration	0-79	41	0-10	4	53	Aspirated every 12 hours, 5th and 6th days; pressure 6 cm. H_2O and 20 c.c. withdrawn 24 hr. before death	Died after 8 days; 1 to 2 mm. perforation of pouch at superior end, acute generalized peritonitis

there was only one instance of perforation distant from the suture line. In an attempt to remove this factor the clamp was omitted in two cases. The results were not conclusive, thus a second group of operations was performed in which healing was complete in five-sixths of the pouch before closure. In no case of secondary closure was the perforation near either the new or the old suture line, thus eliminating the question of surgical trauma as a possible cause of the ulcer formation and perforation.

Two etiologic factors remained to explain the cause of the ulcers. The first was the action of normal gastric juice in continuous contact with the gastric mucosa. The second was pressure within the pouch which would tend to interfere with venous return and possibly cause stasis of blood flow leading to ulceration.

It is possibly of significance that in one case (Dog 9) an ulcer did not occur after twenty days in spite of marked distention of the pouch. Unfortunately, the contents of this pouch escaped before a measurement of pressure or a determination of acidity could be made.

Sperling and Wangensteen[6] subjected closed ileal loops in the dog to sustained increases of intraluminal pressure and showed that when a pressure of 40 cm. of water was employed, the bowel showed necrotic areas after seventeen to twenty hours and was abnormally permeable and nonviable. Twenty to thirty centimeters of water produced similar changes, but required a longer period of time.

Burget and his co-workers[7] found that dogs with closed jejunal loops can be kept alive for long periods of time provided the pressure in the loops is kept down by aspiration of the fluid.

The studies in Group III reduce to a minimum the factor of increased pressure as a possible cause of perforation. The average pressure (which approximates average maximal pressure, for each reading would be close to maximum for the preceding twelve to twenty-four hour period) was in all cases less than 30 cm. of water. As shown in Table III, Dogs 26 and 31 had lower pressures, but higher free-acid values than Dogs 29 and 30. The former developed ulcers, whereas the latter did not. Driver and co-workers[10] have demonstrated that an increase of intraluminal pressure from 0 to 45 cm. of H_2O greatly enhanced the ulcerogenic action of acid pepsin in the jejunum. Even with frequent aspiration, some pressure developed in the closed pouches. That this low pressure may have been an essential factor in perforation is a possibility which cannot be excluded.

Insertion of the needle into the pouch introduced mechanical trauma as a possible cause of ulceration. However, in all cases of ulcer formation in Group III, the ulcer was in the superior end of the pouch and not near the puncture site at the peritoneal attachment. The area of mucosa which had been repeatedly punctured during aspirations presented no detectable change.

Clinically, conditions approaching those encountered in a closed pouch are found in pyloric stenosis; the increased pressure and increased secretory activity[11] often present in this condition may predispose to extension or perforation of an ulcer.

SUMMARY

In Group I, primary closure of the Heidenhain pouch in five dogs resulted in acute ulcer formation with perforation in all cases.

In Group II, secondary closure of the Heidenhain pouch in eight dogs resulted in acute ulcers with perforation in four cases. Three died of extraneous causes and one that was sacrificed after twenty days showed no pathologic change.

In Group III, primary closure of the Heidenhain pouch with daily aspiration of the pouch resulted in acute ulcer with perforation in four of six dogs. Two died of other causes without pathologic change of the pouch. All those in which the free acid averaged over 40 had ulcers of the pouch with perforation.

The method used in Group III may prove of value in the study of secretory pressure of the gastric glands.

CONCLUSIONS

In the majority of cases, acute ulcers with perforation develop in closed Heidenhain gastric pouches. The relative importance of acid pepsin and high intralumenal pressure in the genesis of these ulcers is discussed.

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AN UNDERWATER DRAINAGE BOTTLE STAND

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EXPERIENCE has demonstrated that closed drainage of the thorax is maintained most effectively through the use of a water seal. The typical water seal closed system usually is comprised of two appropriately connected bottles, one (the catch bottle) serving to collect fluid which drains from the thorax and the other functioning as the water seal to prevent entry of air into the pleural cavity. Both bottles commonly are placed on the floor, near the patient's bed, where they constantly are in danger of being accidentally overturned or disconnected from one another or from the patient. Untrained personnel have a tendency to lift the bottles from the floor for inspection, with the result that fluid may be aspirated from the seal bottle into the catch bottle and the water seal thereby broken.

While working in an Overseas Thoracic Center, with a frequently changing and at times inadequately trained staff of ward attendants, I devised a bottle stand which simplified the maintenance of an effective water seal to the point of making it practically foolproof. Once in operation, the drainage apparatus required no attention other than to empty the catch bottle as required, and periodically to replace the small amount of water lost from the seal bottle by evaporation. The following are the chief items required for construction of the stand:

(1) Several short lengths of board (¾ inch thick)

(2) Two strips of steel (25½ by 1¼ by ⅛ inch)

(3) Two cylindrical, wire test-tube baskets (5 inches in diameter and 6 inches high)

A wooden base is constructed by nailing the ¾ inch boards together to form a simple square platform measuring 20 by 20 inches. Each 25½ inch metal strip is bent to a right angle, one arm measuring 24 inches in length and the other 1½ inches. An opening (3/16 inch in diameter) is drilled in the 24 inch arm, at a point 1 inch from the free end. A second drill hole is made 5 inches from the free end. A third opening is drilled 19 inches from the free end. Drill holes are made in the 1½ inch arm, at points ½ and 1 inch from the free end, respectively (Fig. 1, *A*).

The 24 inch metal arms are placed vertically, parallel to one another and 5 inches apart, over the central portion of the wooden base. These uprights are secured to the base by screws which pass through the two drill holes previously made in the 1½ inch transverse arms. The upper wire basket is placed between the uprights and is bolted in position with its base lying 18 inches

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above the wooden platform. (The bolts, fitted with large washers, pass through the openings previously drilled 1 and 5 inches from the upper ends of the uprights.) The lower basket is placed directly on the wooden platform, between the uprights, and is fixed in position by bolts which pass through the lowermost openings in the uprights. The stand now is complete and is ready to receive the bottles (Fig. 1, *B*).

Discarded Vacoliter bottles (1000 c.c.) are used, and will be found to fit into the baskets snugly. The bottles are connected, as shown in Fig. 2. The lower (water seal) bottle is securely wired or taped to its basket and remains in position permanently. The upper (catch) bottle is removable, for purposes of emptying. Fig. 3 shows the apparatus (old model) in use.

The setup described has the following advantages:

1. The base is sufficiently stable to prevent the apparatus from being accidentally overturned.

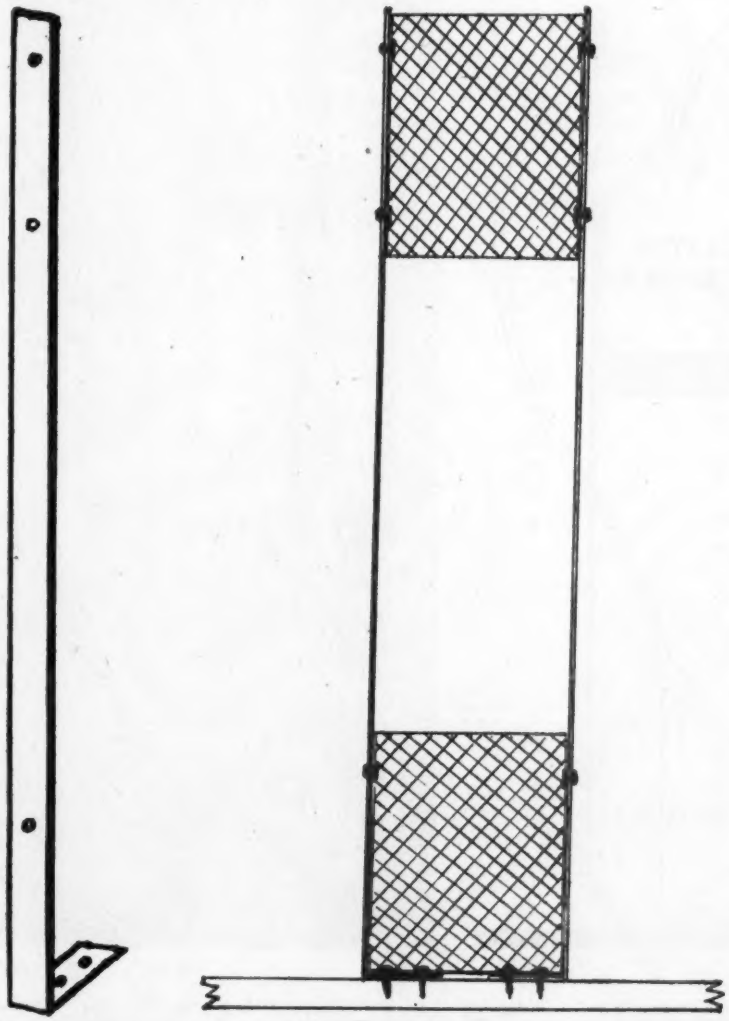

Fig. 1.—*A*, Metal upright with drill holes in vertical and transverse arms. *B*, Diagrammatic side view of bottle stand. Metal uprights are fixed to wooden base by screws. Wire baskets are bolted to uprights through drill holes shown in *A*.

2. The fact that the catch bottle is supported only a short distance below the level of the patient makes it unnecessary to use a long connecting tube which is apt to become kinked and thus interfere with drainage.

3. The amount of drainage in the catch bottle can be read at a glance, directly from the calibrations on the Vacoliter flask.

4. The hydraulic resistance of the water seal remains constant for, regardless of the amount of thoracic drainage into the catch bottle, there is no entry of

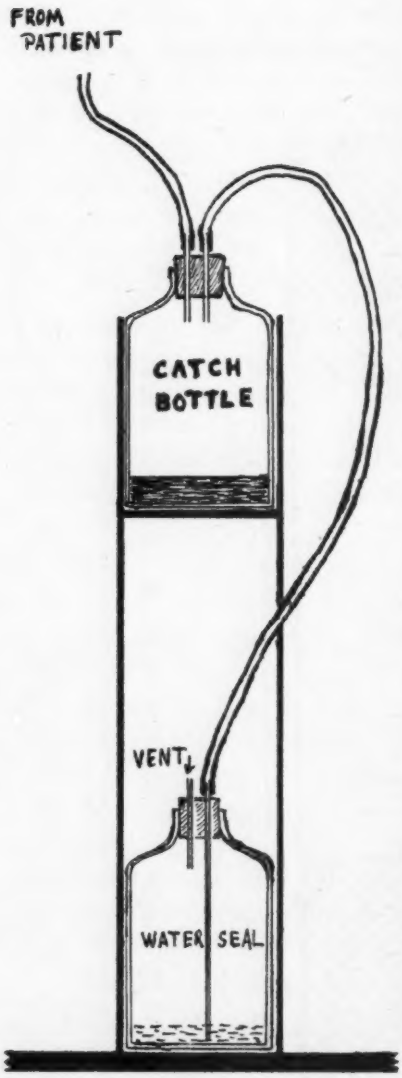

Fig. 2.

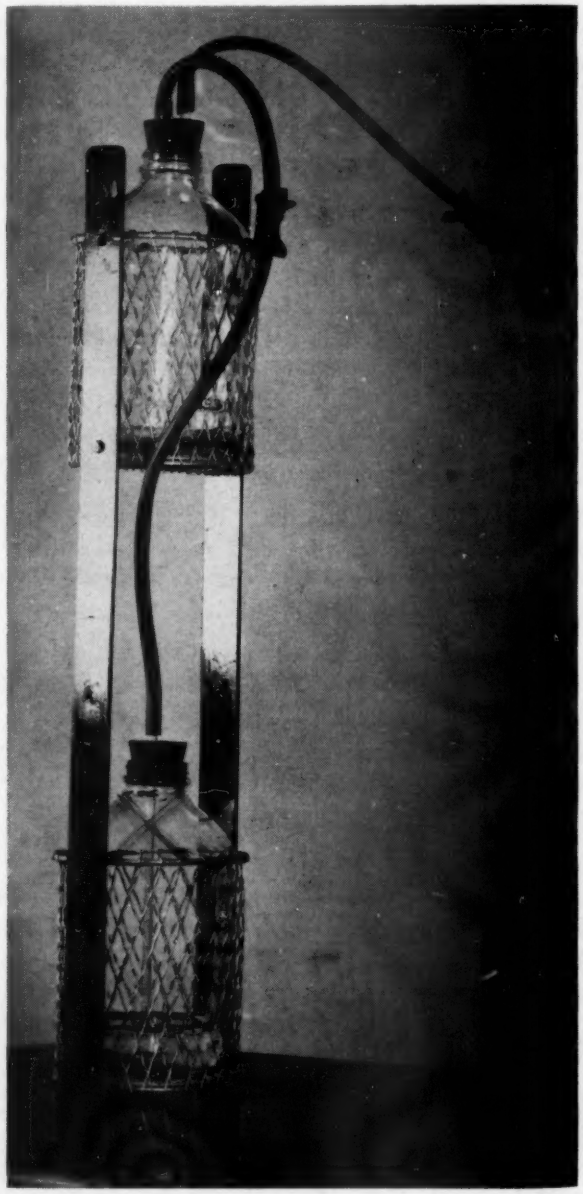

Fig. 3.

Fig. 2.—Diagrammatic side view of bottles showing connections. Stopper of catch bottle bears two short glass tubes. Stopper of water-seal bottle bears one long and one short glass tube. Long tube is immersed in water for a distance of only ¼ to ½ inch. Water-seal bottle is wired in place.

Fig. 3.—Apparatus (old model) in use.

drainage fluid into the water seal bottle. (The long tube of the seal bottle should be immersed in water for a distance of only ¼ to ½ inch. Deeper immersion results in retardation of drainage from the chest).

5. The bottles are maintained in a fixed position which prevents them from being inadvertently torn apart and the closed system thereby broken.

6. The height differential between the top of the catch bottle and the water seal is approximately 50 cm. which is sufficient to prevent aspiration of fluid from the seal bottle into the catch bottle, and breaking of the seal on violent inspiration.

7. The lower (seal) bottle, being wired in place, cannot be elevated to a dangerous level by an uninitiated attendant thereby permitting its fluid to be aspirated into the catch bottle and the seal thus broken.

8. If desired, the entire stand can be elevated for inspection of both bottles without influencing the height differential between them and running the risk of breaking the seal. Furthermore, if the stand is elevated there is no danger of fluid in the catch bottle being aspirated into the pleural cavity.

9. Negative pressure can be readily applied to the system if desired, merely by connecting a suction apparatus to the vent in the water seal bottle.

Personal experience over a period of two years demonstrated the apparatus to be eminently satisfactory in maintaining an effective water seal under circumstances which at times permitted only minimal supervision.

Case Reports

BENIGN FIBROMUCOUS POLYP OF THE URETER

Report of a Case

James K. Palmer, M.D.,* and Laurence F. Greene, M.D. † Rochester, Minn.

Vest,‡ in 1945, reported that he was able to find only seventy odd cases of ureteral tumor which were considered to be benign. Of these tumors, he estimated that 60 per cent occurred in the lower part of the ureter and that 30 to 35 per cent protruded from the ureteral orifice. The diagnosis of these tumors, as described in the literature, is based on the clinical symptoms of renal or ureteral pain, with or without extension and, in some instances, gross hematuria. The hematuria may be microscopic, and in some cases a hydronephrotic kidney secondary to the ureteral tumor may be palpable. Roentgenographic studies may disclose a filling defect in the excretory or retrograde urogram, and minimal or marked hydronephrosis. In some cases a mass protruding from one of the ureteral orifices may be seen by cystoscopic examination. Unilateral hematuria and obstruction or bleeding at a localized point on attempted passage of a ureteral catheter may also be noted. Careful microscopic examination of the excised lesion is necessary to establish the benign nature of the tumor. Because of the relatively infrequent occurrence of such benign lesions of the ureters we report the following case.

REPORT OF A CASE

The patient, a woman 34 years old, complained of intermittent episodes of gross hematuria of nine years' duration. During this period she had had fifteen episodes of gross hematuria, each of which had lasted four or five days, the last episode occurring three months before admission to the Mayo Clinic. She described one attack of excruciating pain in the right lumbar region which extended to the groin and required narcotics for relief. She had had episodes of urinary urgency and frequency for as long as she could remember. The remainder of her history and the results of physical examination were noncontributory; neither kidney was palpable.

Results of routine laboratory studies were normal or negative. Urinalysis was reported to disclose pyuria of grade 1 (on the basis of 1 to 4). An excretory urogram was made and interpreted as revealing nothing abnormal. At first glance, the bladder and both ureteral orifices seemed normal in cystoscopic examination. However, study of the right ureteral orifice disclosed a narrow polypoid lesion, 0.75 cm. in diameter, which, with each ejaculation of urine, protruded 1.5 cm. into the bladder from the right ureteral orifice. The gross appearance of the polyp suggested a benign lesion. The right ureter was easily catheterized. A right pyelo-ureterogram was made (Fig. 1). This was interpreted as indicating that the right kidney and ureter were normal, except that poor visualization of the lowermost portion of the ureter suggested that it was dilated.

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*Fellow in Urology, Mayo Foundation.
†Section on Urology, Mayo Clinic.

‡Vest, S. A.: Conservative Surgery in Certain Benign Tumors of the Ureter, J. Urol. 53: 97-121, 1945.

Fig. 1.

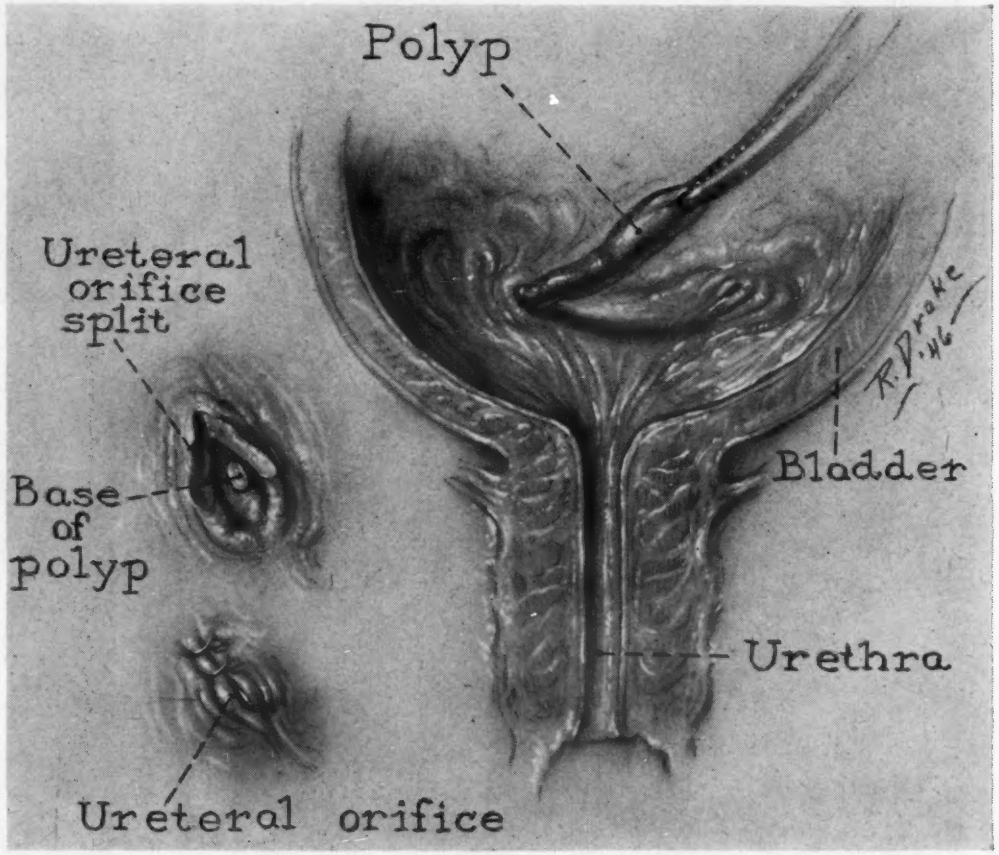

Fig. 2.

Fig. 1.—Preoperative right retrograde pyelogram, showing dilatation of the lower part of the ureter.
Fig. 2.—The surgical procedure employed in this case.

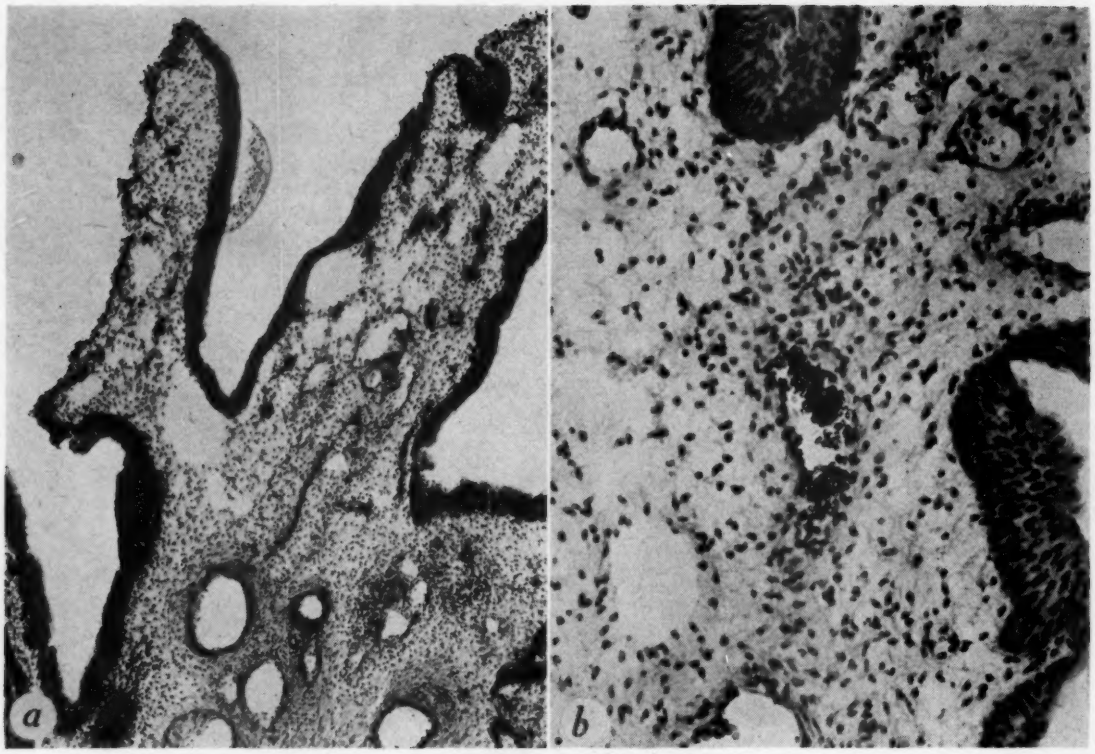

Fig. 3.—Low (*a*, ×45) and high (*b*, ×160) magnification of tissue from the ureteral polyp. The polyp was lined by squamous and transitional epithelium thrown into papillary folds, and was comprised of very vascular myxomatous connective tissue (hematoxylin and eosin stain).

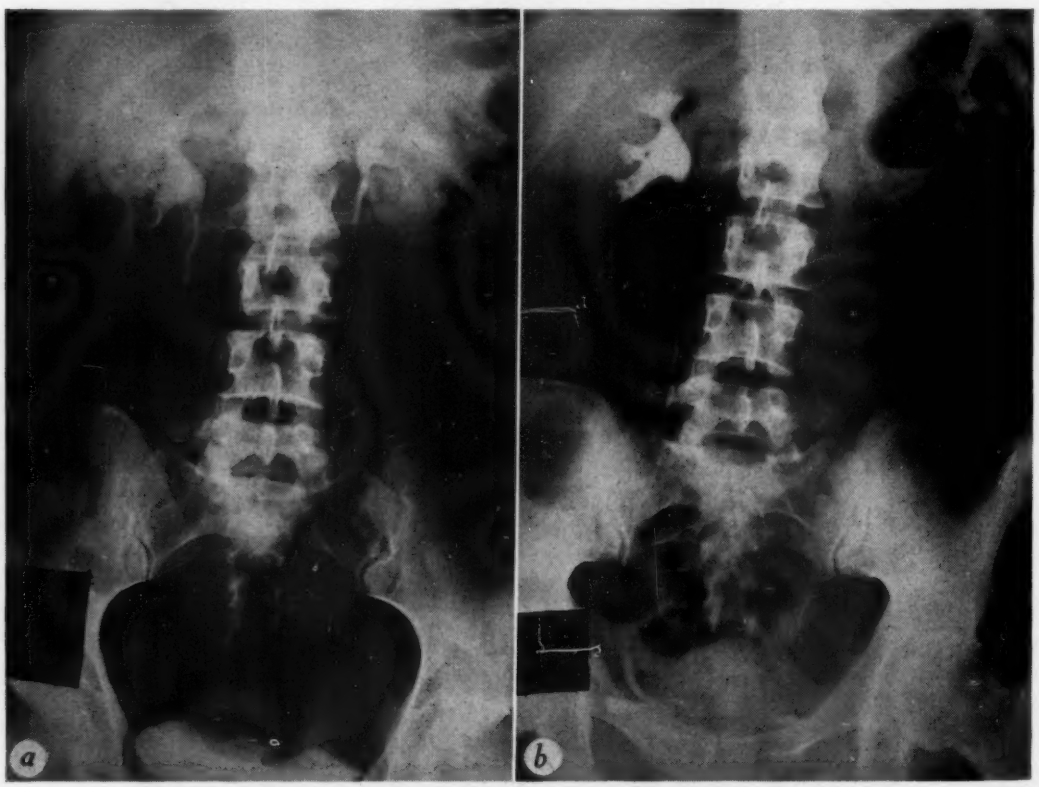

Fig. 4.—*a*, Postoperative excretory urogram, showing normal urinary tract; *b*, postoperative right retrograde pyelogram.

Transvesical excision of the polyp was advised and carried out. The bladder was opened in the midline. The polyp could be seen periodically projecting from the right ureteral meatus. At times, this polyp was completely retracted up the ureter. A small curved hemostat was passed up the right ureter, and the polyp was grasped and pulled down until its base appeared near the ureteral meatus (Fig. 2). The meatus was then incised upward for 1 cm. to expose the base of the polyp (Fig. 2). The polyp was then completely excised and the ureteral meatus was reconstructed with two catgut stitches (Fig. 2). The bladder was closed about a No. 26 French cystostomy tube.

The specimen consisted of a polypoid lesion 4 by 0.7 cm. Multiple sections were made and examined microscopically. These showed benign fibromucous tissue covered with normal squamous epithelium (Fig. 3, *a* and *b*).

The patient withstood the surgical procedure well. Convalescence was uneventful.

At our request the patient returned nine months later for re-examination. Her health had been perfect and she had no urinary symptoms. The urinary tract was studied by means of excretory urography, cystoscopy, and retrograde pyelography, and was considered to be normal (Fig. 4, *a* and *b*.)

UNILATERAL, CONGENITAL SYNOSTOSIS OF LUNATE AND TRIANGULAR BONES

GEORGE HAMMOND, M.D., SAYRE, PA.

(From the Section on Orthopedic Surgery, Guthrie Clinic and Robert Packer Hospital)

CONGENITAL fusion of carpal bones is not common and the infrequency of synostosis of the lunate and triangular bones warrants the following case report.

CASE REPORT

A white, American soldier, aged 20 years, was admitted to the 298th General Hospital, U. S. Army, on June 18, 1945, complaining of a fracture of the fifth metacarpal of the left hand. On June 5, 1945, a rifle which he was cleaning accidentally discharged and caused a perforating wound of the left hand. X-ray examination revealed a comminuted fracture of the proximal shaft and base of the fifth metacarpal. On June 6, 1945, débridement was done and a short arm cast was applied.

Fig. 1.—Anteroposterior and oblique roentgenograms of the left wrist showing the carpal anomaly.

A review of the x-ray films revealed that, in addition to the fracture described, there was an interesting anomaly of the carpus, consisting of fusion of the lunate and triangular bones (Fig. 1). Roentgenogram of the right wrist did not reveal a similar synostosis.

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Detailed questioning of the patient failed to disclose any symptoms referable to the left wrist prior to wounding.

A review of the literature reveals the following points of interest concerning this carpal anomaly: Congenital synostosis of the triangular and lunate bones causes no symptoms and cannot be recognized by clinical examination. Most cases are discovered accidentally in roentgenograms taken for other conditions. It most commonly occurs bilaterally. The fusion is generally complete rather than partial. Synostosis of tarsal bones may accompany. The frequent symmetrical distribution of synostoses of the carpus and tarsus, their association with synostoses or aplasia of the interphalangeal joints, and the familial occurrence of these anomalies tend to indicate a congenital and hereditary character of the lesions.

Most authors agree that the underlying cause is an absence or imperfect differentiation of the intermediary zone in the development of the ossification centers for the carpus. Fusion of such bones is a result of hypoplasia or aplasia of the individual articulations.

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Book Reviews

Cancer—Diagnosis, Treatment, and Prognosis. By Lauren V. Ackerman and Juan A. del Regato. Pp. 1115, with 745 illustrations and 42 color reproductions. St. Louis, 1947, The C. V. Mosby Company.

The work by Ackerman and Regato is excellently done. It is rather difficult for the reviewer to see how a consideration of so broad a subject as cancer could be so well handled. Malignant diseases involving the various regions of the body are very carefully considered from the standpoint of etiology, symptomatology, treatment, and prognosis. It is remarkable, also, how judicial the authors have been in evaluating the various forms of therapy, particularly surgery and irradiation. The volume is profusely illustrated not only with photographs of lesions and x-rays, which are well reproduced, but also colored photographs of lesions. An important part of the book is the diagrammatic demonstration of the lymph drainage of each malignant lesion discussed. The work is particularly valuable from the standpoint of teaching and of value to the clinician in handling the patient with malignant disease. In addition to the specific consideration of treatment in each type of malignancy, a chapter is devoted to the general consideration of surgery of cancer and another one to radiotherapy of cancer. These are concerned primarily with the broad application of these two therapeutic agents. Appended to each chapter is an excellent bibliography which is quite complete.

After a careful review of this volume, it is difficult to say if there is any one part that is better than the others. Every subject seems to be well handled and thoroughly covered. This is a book which should be in the hands of every practitioner who is concerned with the diagnosis and treatment of malignancy. In fact, every doctor could well afford to have this in his library because of its value as a reference book.

BOOKS RECEIVED

The receipt of books is acknowledged in this section and this treatment must be regarded as sufficient acknowledgment of the courtesy of the senders. Selections will be made for more extensive review dictated by the interests of our readers and as space permits.

HARVEY CUSHING, A BIOGRAPHY. By John F. Fulton, M.D., Sterling Professor of Physiology, Yale University. Cloth. Pp. 718, with 150 illustrations. Springfield, Ill., 1946, Charles C Thomas, Publisher.

DIAGNOSIS AND TREATMENT OF MENSTRUAL DISORDERS AND STERILITY. By Charles Mazer, M.D., Assistant Professor of Gynecology and Obstetrics, University of Pennsylvania, and S. Leon Israel, M.D., Instructor, University of Pennsylvania, Cloth. Price $7.50. Pp. 513, with 133 illustrations. New York, 1946, Paul B. Hoeber, Inc.

SURGICAL TREATMENT OF SOFT TISSUES. By Frederic W. Bancroft, M.D., F.A.C.S., Associate Clinical Professor of Surgery, Columbia University, and George H. Humphreys, M.D., F.A.C.S., Valentine Mott Professor of Surgery, Columbia University. Cloth. Price $15. Pp. 501, with 244 illustrations. Philadelphia, 1946, J. B. Lippincott Company.

URGENT SURGERY, Volume I. By Julius L. Spivack, M.D., LL.D., Associate Professor of Surgery, University of Illinois. Cloth. Price $10. Pp. 676, with 572 illustrations. Springfield, Ill., 1946, Charles C Thomas, Publisher.

NEUROANATOMY. By Fred A. Mettler, Ph.D., Professor of Anatomy, University of Georgia School of Medicine. Cloth. Pp. 384, with 337 illustrations. St. Louis, 1946, The C. V. Mosby Company.

CURRENTS IN BIOCHEMICAL RESEARCH. By David E. Green, Chief of the Enzyme Laboratory, Columbia University, Editor. Cloth. Price $6. Pp. 486, with no illustrations. New York, 1946, Interscience Publishers, Inc.

INTRODUCTION TO SURGERY. By Virginia Kneeland Frantz, M.D., Associate Professor of Surgery, Columbia University, and Harold Dortic Harvey, M.D., Assistant Professor of Clinical Surgery, Columbia University. Cloth. Pp. 208, with 11 illustrations. New York, 1946, Oxford University Press.

PENICILLIN IN NEUROLOGY. By A. Earl Walker, M.D., Associate Professor, and Herbert C. Johnson, M.D., Resident Neurological Surgeon, University of Chicago. Cloth. Price $5. Pp. 177, with 72 illustrations. Springfield, Ill., 1946, Charles C Thomas, Publisher.

OUTLINE OF THE SPINAL NERVES. By John Favill, A.B., M.D., F.A.C.P., Clinical Professor of Neurology (Rush), University of Illinois. Cloth. Price $3.75. Pp. 190, with 12 illustrations. Springfield, Ill., 1946, Charles C Thomas, Publisher.

THE COMPLEAT PEDIATRICIAN. By W. C. David, M.D., Professor of Pediatrics, Duke University, School of Medicine. Cloth. Price $3.75. Pp. 256, with no illustrations. Durham, N. C., 1946, Duke University Press.

POSTGRADUATE OBSTETRICS. By William F. Mengert, M.D., Professor of Obstetrics anl Gynecology, Southwestern Medical College. Price $5. Pp. 363, with 123 illustrations. New York, 1947, Paul B. Hoeber, Inc.

AN INTEGRATED PRACTICE OF MEDICINE. FOUR VOLUMES AND INDEX. By Harold Thomas Hyman, M.D., Cloth. Pp. 4131, with 1184 illustrations. Philadelphia, 1947, W. B. Saunders Company.

PARENTERAL ALIMENTATION IN SURGERY. By Robert Elman, M.D., Associate Professor of Clinical Surgery, Washington University School of Medicine. Cloth. Price $4.50. Pp. 267, with 31 illustrations. New York, 1947, Paul B. Hoeber, Inc.

GYNECOLOGICAL AND OBSTETRICAL PATHOLOGY. By Emil Novak, A.B., M.D., D.Sc., F.A.C.S., Associate in Gynecology, Johns Hopkins Medical School. Cloth. Pp. 555, with 542 illustrations. Philadelphia, 1947, W. B. Saunders Company.

HEPARIN IN THE TREATMENT OF THROMBOSIS. By J. Erik Jorpes, M.D., Reader in Biochemistry, Caroline Institute, Stockholm, Sweden. Cloth. Price $6.50. Pp. 239, with 21 illustrations. New York, 1947, Oxford University Press.

PHYSICAL MEDICINE IN GENERAL PRACTICE. By Arthur L. Watkins, M.D. Cloth. Price $5. Pp. 330, with 8 illustrations. Philadelphia, 1947, J. B. Lippincott Co.

RADICAL SURGERY IN ADVANCED ABDOMINAL CANCER. By Alexander Brunschwig, M.D., Professor of Surgery, University of Chicago. Cloth. Price $7.50. Pp. 318, with 117 illustrations. Chicago, 1947, University of Chicago Press.

FUNDAMENTALS OF CLINICAL NEUROLOGY. By H. Houston Merritt, M.D., Professor of Clinical Neurology, College of Physicians and Surgeons, Columbia University, Fred A. Mettler, M.D., Associate Professor of Anatomy, Columbia University, Tracy Jackson Putnam, M.D., Professor of Neurology and Neurological Surgery, Columbia University. Cloth. Pp. 261, with 95 illustrations. Philadelphia, 1947, The Blakiston Company.

TECHNIQUES AND PROCEDURES OF ANESTHESIA. By John Adriani, M.D., Clinical Assistant Professor of Surgery, Louisiana State University. Cloth. Price $6. Pp. 372, with 122 illustrations. Springfield, Ill., 1947, Charles C Thomas, Publisher.

MEDICINE IN THE CHANGING ORDER. By New York Academy of Medicine, Committee on Medicine and the Changing Order. Cloth. Price $2. Pp. 282, with no illustrations. New York, 1947, Commonwealth Fund.

A SYNOPSIS OF SURGICAL ANATOMY. By Alexander Lee McGregor, M.Ch., F.R.C.S., Surgeon, Johannesburg General Hospital. Cloth. Price $6.50. Pp. 671, with 699 illustrations. Baltimore, 1946, Williams & Wilkins Company.

CLEFT PALATE AND SPEECH. By Muriel E. Morley, B.Sc., F.C.S.T., Speech Therapist to Royal Victory Infirmary. Cloth. Price $3. Pp. 154, with 52 illustrations. Edinburgh, 1945, E. & S. Livingstone.

EYE SURGERY. By H. B. Stallard, M.B.E., M.D., F.R.C.S., Eye Surgeon, Radium Institute and Mount Vernon Hospital. Cloth. Price $11. Pp. 432, with 338 illustrations. Baltimore, 1946, Williams & Wilkins Company.

SURGERY OF THE HAND. By R. M. Handfield-Jones, M.C., M.S., F.R.C.S., Examiner in Surgery, Universities of Cambridge. Cloth. Price $5.50. Pp. 156, with 104 illustrations. Baltimore, 1946, Williams & Wilkins Company.

COLOR ATLAS OF HEMATOLOGY. By Roy R. Kracke, M.D., Dean and Professor of Clinical Medicine, Medical College of Alabama. Cloth. Price $5. Pp. 197, with 35 illustrations. Philadelphia, 1947, J. B. Lippincott Company.

SURGICAL PATHOLOGY. By William Boyd, M.D., Professor of Pathology, University of Toronto. Cloth. Pp. 820, with 530 illustrations. Philadelphia, 1947, W. B. Saunders Company.

GYNECOLOGY WITH A SECTION ON FEMALE UROLOGY. By Lawrence R. Wharton, Ph.D., M.D., Assistant Professor of Gynecology, Johns Hopkins Medical School. Cloth. Pp. 1,000, with 479 illustrations. Philadelphia, 1947, W. B. Saunders Company.

DISEASES OF THE CHEST WITH EMPHASIS ON X-RAY DIAGNOSIS. By Eli H. Rubin, M.D., Attending Physician, Division of Pulmonary Diseases, Montefiore Hospital, New York, and Morris Rubin, M.D., Assisting Visiting Surgeon, Triboro Hospital, New York. Cloth. Pp. 667, with 355 illustrations. Philadelphia, 1947, W. B. Saunders Company.

SURFACE AND RADIOLOGICAL ANATOMY. By A. B. Appleton, M.D., Professor of Anatomy, University of London, W. J. Hamilton, M.D., Regius Professor of Anatomy, University of Glasgow, G. Simon, M.D., Demonstrator, Radiological Anatomy, St. Bartholomews Hospital, London. Cloth. Price $7. Pp. 321, with 390 illustrations. Baltimore, 1946, Williams & Wilkins Company.

PYE'S SURGICAL HANDICRAFT. By Hamilton Bailey, M.D., Surgeon, Royal Northern Hospital, London. Cloth. Price $7. Pp. 641, with 789 illustrations. Baltimore, 1947, Williams & Wilkins Company.

A MANUAL OF FRACTURES AND DISLOCTIONS. By Barbara B. Stimson, A.B., M.D., Assistant Professor of Clinical Orthopedic Surgery. Cloth. Price $3.25. Pp. 207, with 98 illustrations. Philadelphia, 1947, Lea & Febiger.

THE PATHOLOGY OF TRAUMATIC INJURY. By James V. Wilson, M.D., Pathologist to Harrogate Hospital. Cloth. Price $6. Pp. 182, with 61 illustrations. Baltimore, 1946, Williams & Wilkins Company.

CINEPLASTY. By Henry H. Kessler, M.D., Ph.D. Cloth. Price $6.75. Pp. 314, with 199 illustrations. Springfield, Ill., 1947, Charles C Thomas, Publisher.

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